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1929

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A CLINICAL AND BACTERIOLOGICAL STUDY OF 113 CASES OF STREPTOCOCCIC PUERPERAL INFECTION

JOHN W. HARRIS, M.D. AND J. HOWARD BROWN, PH.D.

From the Departments of Obstetrics and of Pathology and Bacteriology, the Johns Hopkins Hospital and University

For a number of years it has been the routine custom in the Obstetrical Service of the Johns Hopkins Hospital to make bacteriological studies of the lochia in all patients who present rises in temperature to 101°F. or higher on two successive days during the first ten days of the puerperium, as well as in all cases of incomplete abortion and intrapartum infection requiring operative intervention. In the latter material is taken for culture before a vaginal examination is made or the operation is begun.

METHOD OF CULTURE

In obtaining uterine lochia for culture we have employed the following technique: The external genitalia are thoroughly painted with a 2 per cent alcohol-acetone solution of mercurochrome. After widely separating the labia, the cervix is exposed by means of a small, sterile, bivalve speculum and is wiped dry with sterile gauze sponges. A sterile glass lochial tube of the type descriped by Little (1) is then inserted into the uterine cavity and carried to the fundus. After being filled with lochia it is removed, wrapped in a sterile towel, and immediately taken to the laboratory. The tube is then broken by means of a file and only the middle of the column of lochia is used for bacteriological study. After smears have been made, the following media are inoculated: aerobic, human blood agar plates, human blood agar slants sealed under reduced oxygen tension; aerobic, human serum bouillon and cooked meat medium sealed with vaseline. These media, and especially the last, we have found to give excellent primary growths of the various bacteria, both aerobic and anaerobic, usually found in the uterine cavity.

From June 9, 1926 to August 29, 1927, samples of lochia were taken

from 168 patients and subjected to bacteriological study. The results of these cultures are as follows:

Organisms	*Number of cases*
Streptococci (pure)	19
Streptococci and other organisms	94
Diphtheroids (pure)	14
Diphtheroids and other organisms	14
Colon bacilli and other organisms	8
Saprophytes	2
Gonococci (pure)	1
Sterile	16
Total	168

Thus, it is seen that of the 168 uterine cultures 113, or 67 per cent, contained streptococci either in pure culture or in association with other organisms. From these 113 cultures we have isolated and studied 116 strains of streptococci, since each of three cultures contained two strains of the infecting organism. Of these 113 cultures two were taken at the time of operation in cases of intrapartum infection, eleven were made before the completion of incomplete abortions, and one hundred were obtained from women with clinical manifestations of puerperal infection.

ABORTIONS

The clinical data in the eleven cases of incomplete abortion in which streptococci were found in the uterine cavity are presented in Table I. It should be stated that in all of these patients bleeding was so profuse that active interference was necessary. The table shows that the predominant bacteria in seven of the eleven cases were aerobic, beta-hemolytic streptococci; in two, aerobic, non-hemolytic streptococci; while in the remaining two the infecting organisms were anaerobic streptococci, one of which was of the beta-hemolytic variety.

Ten of the eleven patients recovered and in only one of the ten did the infection extend beyond the uterus. In this instance (S58) bilateral pelvic thrombophlebitis developed, involving both pelvic veins, and recovery followed ligation of the affected veins. A detailed account of this case appeared in *The Bulletin of the Johns Hopkins Hospital* for July, 1928. In only two of the remaining patients who recovered did the temperature remain elevated for more than six days and none of them were seriously ill.

The single death in the abortion series complicated by streptococcic infection occurred in a 17-year-old white girl, who during the third month of pregnancy had inserted a hat-pin into the uterus. Three days later she was admitted to the hospital bleeding profusely, and with signs of beginning peritonitis—temperature 102°F., pulse 134. Owing to the profuse bleeding digital curettage was done and a number of placental fragments removed. Upon histological examination these showed pronounced acute infection of the decidua, and sections stained for bacteria revealed many cocci in chains. The day after admission the signs of peritonitis became more pronounced and the patient died on the twentieth day. Repeated blood cultures were negative. A uterine culture taken before the completion of the abortion showed an aerobic, beta-hemolytic streptococcus and *B. welchii*. At autopsy there was found a generalized peritonitis with localized collections of pus between the folds of the intestines and between the intestines and liver and spleen. There was no sign of perforation of the uterus.

OPERATIVE DELIVERIES

Table II shows that in 28 of the 113 patients the labor was terminated by the following operative procedures:

Low forceps	11
Mid forceps	4
Manual dilatation of cervix and mid forceps	2
Manual dilatation of cervix and high forceps	1
Breech extraction	2
Version and extraction	1
Insertion of bag	3
Bag followed by version and extraction	1
Manual dilatation of cervix and craniotomy	2
Embryotomy	1
Total	28

When Table II is studied, it is seen that extension of infection beyond the uterus occurred in two patients. In one (S33) the labor was complicated by premature rupture of the membranes and by a prolonged labor which was terminated by low forceps. The patient developed an infection due to an aerobic, beta-hemolytic streptococcus which involved the broad ligaments with unilateral abscess formation.

TABLE I

Clinical data and bacteriological findings in 11 cases of infected abortion

BACTERIOLOGICAL NUMBER	RACE	DURATION OF PREGNANCY	TEMPERATURE AT OPERATION	DURATION OF FEVER	HIGHEST TEMPERATURE		COMPLICATIONS	RESULT	UTERINE CULTURE
					Degrees	Day of highest temperature			
				days					
S6	W.	3 months	101.6	4	101.8	2d	None	Excellent	Aerobic, beta-hemolytic streptococci *Staph. albus*
S11	W.	3 months	101	3	101.2	2d	None	Excellent	Aerobic, beta-hemolytic streptococci Aerobic, alpha-hemolytic viridans streptococci Aerobic, non-hemolytic diphtheroid *Staph. albus*
S75	W.	2 months	104	4	104	1st	None	Excellent	Aerobic, beta-hemolytic streptococci *B. welchii. B. coli communis* Anaerobic, non-hemolytic diphtheroid
S86	W.	6 weeks	103	16	103.2	5th	None	Excellent	Aerobic, beta-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S119	B.	2 months	99.2	15	101.6	5th	None	Excellent	Aerobic, beta-hemolytic streptococci Aerobic, non-hemolytic diphtheroid
S58	W.	4 months	102.2	19	105.4	6th	Pelvic thrombophlebitis	Excellent	Aerobic, beta-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S91	W.	3 months	103	20	103	1st	Generalized peritonitis	Death	Aerobic, beta-hemolytic streptococci *B. welchii*

S4	B.	5 months	101.8	5	102	4th	None	Excellent	Aerobic, non-hemolytic streptococci *Staph. albus*
S105	W.	3 months	100.4	6	100.4	1st	None	Excellent	Aerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S113	W.	3 months	101.6	2	101.8	2d	None	Excellent	Anaerobic, beta-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S83	W.	3 months	101.6	2	101.6	1st	None	Excellent	Anaerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid

TABLE II

Clinical data and bacteriological findings in 28 operative deliveries in this series of cases

BACTERIOLOGICAL NUMBER	RACE	DURATION OF LABOR		VAGINAL EXAMINATIONS BEFORE OPERATIONS	PREMATURE RUPTURE OF MEMBRANES	OPERATION		PUERPERIUM				COMPLICATIONS	RESULTS	UTERINE CULTURE
		Total	Second stage			Type	Temperature	Duration of fever	Highest temperature	Day of highest temperature	Day of culture			
		hours	*hours*					*days*						
S33	W.	20½	3	0	20½ hours	Low forceps	N.	73	103.6	6th	6th	Broad ligament abscess	Excellent	Aerobic, beta-hemolytic streptococci
S40	B.	34		0	18 hours	Man. dil. cervix. High forceps	100.2	7	102.4	4th	5th	Intrapartum infection	Excellent	Aerobic, beta-hemolytic streptococci Aerobic, non-hemolytic diphtheroid *Staph. albus*
S55	B.	42	3	2	42 hours	Mid forceps	N.	74	106	12th	4th	Metritis	Excellent	Aerobic, beta-hemolytic streptococci Aerobic, non-hemolytic diphtheroid *Staph. albus*
S89	W.	9	4	1	9 hours	Low forceps	N.	11	101.6	4th	4th	None	Excellent	Aerobic, beta-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S52	W.	50	2	0	0	Mid forceps	N.	3	102	5th	6th	None	Excellent	Aerobic, alpha-viridans streptococci Anaerobic, non-hemolytic diphtheroid
S43	B.	70	1	0	0	Low forceps	N.	9	101	3d	5th	None	Excellent	Aerobic, alpha-prime streptococci Aerobic, non-hemolytic diphtheroid *Staph. albus*
S27	B.	19	1	1	0	Low forceps	N.	6	102.4	4th	5th	None	Excellent	Aerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid *B. coli communis. Staph. albus*
S29	W.	19	4	0	0	Mid forceps	N.	13	102	7th	5th	None	Excellent	Aerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid *B. coli communis*
S36	B.	21	2	1	0	Low forceps	N.	13	104	7th	5th	None	Excellent	Aerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid *B. coli communis*
S41	B.	27		0	0	Man. dil. cervix. Mid forceps	101	5	102	3d	4th	Intrapartum infection	Excellent	Aerobic, non-hemolytic streptococci Anaerobic, alpha-viridans streptococci Aerobic, non-hemolytic diphtheroid *B. coli communis. Staph. albus*
S61	B.	30	1	0	30 hours	Mid forceps	N.	6	101.2	5th	5th	None	Excellent	Aerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid

S104	B.	9	1½	0	0		Low forceps	N.	7	101.2	5th	5th	None	Excellent	Aerobic, non-hemolytic streptococci Aerobic, non-hemolytic diphtheroid *Staph. albus*
S20	W.	18	3	0	0		Low forceps	N.	28	102	9th	6th	Phlegmasia alba dolens	Excellent	Anaerobic, alpha-viridans streptococci
S63	W.	18	2½	2	8	hours	Low forceps	N.	5	101.4	3d	4th	None	Excellent	Anaerobic, alpha-viridans streptococci Anaerobic, non-hemolytic streptococci
S21	B.	4	2½	0	20	hours	Low forceps	N.	3	101.6	4th	5th	None	Excellent	Anaerobic, non-hemolytic streptococci *Staph. albus*
S35	W.	12	2½	0	0		Low forceps	N.	12	103.4	6th	5th	Tamponade of uterus	Excellent	Anaerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S101	B.	21	3½	0	0		Low forceps	N.	9	102.2	6th	6th	None	Excellent	Anaerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S81	B.	48		1	24	hours	Man. dil. cervix. Mid forceps	N.	7	101.8	4th	5th	None	Excellent	Anaerobic, viridans streptococci Anaerobic, non-hemolytic diphtheroid
S85	W.	4	1	1	0		Breech extraction	N.	9	105	4th	4th	None	Excellent	Aerobic, beta-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S37	B.	10	1	0	10	hours	Breech extraction	N.	9	103.8	7th	5th	None	Excellent	Anaerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid *Staph. albus*
S82	W.	22½	1	2	15	hours	Version and extraction	N.	6	101	3d	4th	Compound presentation	Excellent	Aerobic, alpha-viridans streptococci Aerobic, non-hemolytic diphtheroid
S2	B.	12	0	1	12	hours	Bag and version	N.	26	104	6th	6th	Placenta praevia	Excellent	Aerobic, non-hemolytic streptococci
S115	B.	64½	½	2	2		Insertion of bag	101.4	9	103.6	4th	4th	Intrapartum infection	Excellent	Aerobic, beta-hemolytic streptococci
S118	B.	19	½	1	5	hours	Insertion of bag	N.	7	103.8	3d	5th	Placenta praevia	Excellent	Anaerobic, non-hemolytic streptococci Aerobic, non-hemolytic diphtheroid
S70	B.	18		Many	18	hours	Insertion of bag	101.6				At operation	Placenta praevia	Death	Anaerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S96	B.	48	?	Many	5	days	Embryotomy	104.4	10	104.4	1st	At operation	Neglected transverse. Intrapartum infection	Excellent	Aerobic, beta-hemolytic streptococci *Staph. albus*
S99	B.	19		3	19	hours	Man.dil. cervix. Craniotomy	101.6	6	101.6	1st	4th	Intrapartum infection	Excellent	Anaerobic, non-hemolytic streptococci Aerobic, non-hemolytic diphtheroid
S69	B.	15		Many	15	hours	Man. dil.cervix. Craniotomy	104	3	104	1st	At operation	Eclampsia	Death	Aerobic, alpha-viridans streptococci *B. welchii. B. coli communis* Aerobic, non-hemolytic diphtheroid

The abscess was incised and drained and recovery followed. The second patient (S20), who was delivered by low forceps after a second stage of three hours, developed a puerperal infection due to an anaerobic, alpha-viridans streptococcus. This was complicated by phlegmasia alba dolcns involving the right leg, which gradually subsided without further extension.

A third case in the series (S55) deserves special note. This patient was delivered by low forceps on account of prolonged arrest of the head on the perineal floor. Infection due to an aerobic, beta-hemolytic streptococcus followed and resulted in multiple abscess formation in the uterine wall. The uterus was removed by supravaginal amputation on the thirty-third day of the puerperium and the patient recovered after a long convalescence. (For a detailed report of this case see *The Bulletin of the Johns Hopkins Hospital*, July, 1928.)

There were two deaths in the series of 28 patients whose labors were terminated by various operative procedures, and whose uteri contained streptococci. Case S70, a colored, unregistered multipara, thirty years of age, was admitted to the hospital with the history of profuse bleeding for eight hours, due to a partial placenta previa. On admission, the temperature was 101.6°F., pulse 132, cervix 6 cm. dilated. Before the Vorhees' bag was introduced a culture was taken from the uterine cavity. Three hours later the bag was expelled and was followed immediately by the spontaneous delivery of a term, stillborn child. Expression of the placenta was followed by profuse bleeding. The uterus was packed and the usual procedures employed to combat shock, but in spite of this treatment the patient died three hours after delivery. Autopsy was refused. From the uterine culture taken before the insertion of the Vorhees' bag were grown an anaerobic, gamma, non-hemolytic streptococcus and an anaerobic, gamma, non-hemolytic diphtheroid. We regard the fatal outcome in this case as due solely to hemorrhage and shock accompanying a placenta previa partialis, and believe that the presence of bacteria within the uterine cavity in no wise influenced the outcome.

The second death occurred in Case S69. This patient, an unregistered, colored primipara at term, was infected when admitted because of intrapartum eclampsia, after many vaginal examinations had been made by a colored midwife. The patient was in profound coma, tem-

TABLE III

Clinical data and bacteriological findings in 7 spontaneous deliveries followed by infection with various puerperal complications

BACTERIOLOGICAL NUMBER	RACE	DURATION OF LABOR		VAGINAL EXAMINATIONS	PREMATURE RUPTURE OF MEMBRANES	PERINEAL TEARS	PUERPERIUM				COMPLICATIONS	UTERINE CULTURE
		Total	Second stage				Duration of fever	Highest temperature	Day of highest temperature	Day of culture		
		hours	*hours*		*hours*		*days*					
S42	W.	10	½	0	0	0	11	104	4th	5th	Para-metritis	Aerobic, beta-hemolytic streptococci
S47	W.	Admitted to hospital 5 days post partum because of infection					8	103.6	5th	5th	None	Aerobic, beta-hemolytic streptococci *Staph. albus*
S72	B.	Admitted to hospital 3 days post partum because of infection					89	104	15th	3d	Encapsulated peritonitis	Aerobic, beta-hemolytic streptococci Anaerobic, non-hemolytic diptheroid *Staph. albus*
S1	B.	14	½	0	15	0	7	105	4th	2d	Intrapartum infection	Aerobic, non-hemolytic streptococci Aerobic, non-hemolytic diphtheroid
S120	B.	7	½	0	7	0	5	101.6	4th	5th	Tamponade of uterus	Anaerobic, non-hemolytic streptococci Aerobic, non-hemolytic diphtheroid *Staph. albus*
S38	B.	13	½	0	13	0	4	101.2	4th	5th	Postpartum eclampsia	Anaerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S114	B.	3½	½	0	5	1°	22	104.4	5th	4th	Lobar pneumonia	Anaerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diptheroid

perature 104°F., pulse 120. A full-term, dead child presented in L.O.A., with the head at the level of the ischial spines. The cervix was 6 cm. dilated, the membranes intact, while the uterus was unusually tense, scarcely changing in consistence between contractions. When the membranes were ruptured, a large amount of foul-smelling amniotic fluid escaped, accompanied by bubbles of gas. Because of the obvious intrapartum infection it was decided to deliver the patient at once, and after taking an intrauterine culture delivery was effected by manual dilatation of the cervix and craniotomy.

Following delivery the convulsions ceased and the patient soon became conscious. However, the next day signs of lobar pneumonia developed, involving the right lung up to the level of the fourth rib, as well as the base of the left lung. The patient rapidly grew worse and died two days after delivery.

From the culture taken before operation were grown an aerobic, alpha-viridans streptococcus, *B. welchii*, *B. coli communis* and an aerobic, gamma, non-hemolytic diphtheroid. Microscopic examination of the placenta showed acute inflammation of the amnion and chorion, with a thick layer of leucocytes on the decidual surface. Many bacteria, both cocci and bacilli, could be seen in properly stained sections.

At autopsy there were no signs of peritonitis, and cultures from the peritoneum were negative. The tubes, ovaries, broad ligaments and pelvic vessels were free of involvement. Typical focal necroses were present in the liver, the kidneys showed cloudy swelling, while both lungs presented extensive lobular pneumonic consolidation. Cultures from the heart's blood showed a pure culture of *Pneumococcus*, Type IV, and from the lungs the same organism was recovered together with *H. influenzae*.

It seems to us that the death of this patient was directly due to the post-eclamptic pneumonia and it is doubtful what part the uterine infection might have played had she lived longer.

SPONTANEOUS DELIVERIES

Of the 113 patients 74 were delivered spontaneously at term. All of them recovered and were discharged from the hospital in good condition. For convenience in presentation, these cases have been divided into three groups: I. those that presented various complica-

tions during labor or the puerperium; II. those without complications but in whom premature rupture of the membranes occurred, vaginal examinations were made, or perineal lacerations were sustained; and, finally, III. those in whom none of the complicating factors mentioned under II were present.

It is seen from Table III that 6 of the 74 spontaneously delivered patients presented various complications. To these must be added another, who, while presenting no definite complications associated with the infection, was admitted to the hospital, frankly infected, on the third day of the puerperium. Only two of the seven patients showed evidences of extension of the infection beyond the uterus. One of these (S42) was delivered spontaneously after a short labor conducted without vaginal examinations or perineal tear, and in which the membranes did not rupture prematurely. She developed a moderately severe puerperal infection due to an aerobic, beta-hemolytic streptococcus which eventuated in a mild bilateral parametritis. This, however, did not progress to abscess formation but quickly subsided, so that the entire duration of the infection was eleven days. The second patient (S72) was admitted to the hospital, frankly infected, on the fifth day of the puerperium. She developed a huge encapsulated peritonitis from which 2500 cc. of pus were evacuated. Subsequently an embolic pneumonia with empyema developed. The same strain of aerobic, beta-hemolytic streptococcus was recovered from the uterine cavity, as well as from the peritoneal and pleural exudates. The patient eventually recovered after a prolonged convalescence lasting more than three months. A more detailed report of this case has appeared in a former issue of this JOURNAL (July, 1928). The puerperal complications occurring in the last two patients presented in Table III—one, postpartum eclampsia, and the other, lobar pneumonia—were, in all probability, accidental and in no wise influenced by the infection, nor was the infection influenced by them.

Table IV shows that in 42 of the patients delivered spontaneously vaginal examinations were made during labor, or the membranes had ruptured prematurely, or the perineum was lacerated. It should be stated that in the last event an immediate repair was done, which, from the viewpoint of infection, is probably as serious as a vaginal examination. In six of the patients the only deviation from the

TABLE IV

Clinical data and bacteriological findings in 42 patients with febrile puerperia, who were delivered spontaneously, after vaginal examination, or premature rupture of membranes, or with perineal tear

BACTERIOLOGICAL NUMBER	RACE	DURATION OF LABOR		VAGINAL EXAMINATION	PREMATURE RUPTURE OF MEMBRANES	PERINEAL TEARS	PUERPERIUM				UTERINE CULTURE
		Total	Second stage				Duration of fever	Highest temperature	Day of highest temperature	Day of culture	
		hours	*hours*		*hours*		*days*				
S34	W.	36½	½	0	0	II°	5	102.4	3d	5th	Aerobic, beta-hemolytic streptococci *Staph. albus*
S76	B.	20½	2	2	0	0	9	102.8	3d	4th	Aerobic, beta-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S84	B.	13	2	0	0	I°	6	105	5th	5th	Aerobic, beta-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S31	B.	18	1	0	0	II°	4	101.4	5th	6th	Aerobic, beta-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid *Staph. albus*
S95	B.	41	1	3	28	II°	5	103	2d	4th	Aerobic, beta-hemolytic streptococci Aerobic, non-hemolytic diphtheroid *Staph. albus*
S109	B.	4	½	0	11	0	6	104	3d	5th	Aerobic, beta-hemolytic streptococci Aerobic, non-hemolytic diphtheroid *Staph. albus*
S14	W.	5	1	0	0	I°	10	102	5th	5th	Aerobic, alpha-viridans streptococci
S15	B.	5	1	0	0	II°	4	101	4th	5th	Aerobic, alpha-viridans streptococci Aerobic, non-hemolytic diphtheroid
S51	W.	20	½	0	0	I°	5	101.4	4th	4th	Aerobic, alpha-viridans streptococci Aerobic, non-hemolytic diphtheroid

S9	B.	38	½	0	0	I°	3	101.4	4th	5th	Aerobic, alpha-viridans streptococci Aerobic, non-hemolytic diphtheroid *Staph. albus*
S7	B.	20	½	0	19	I°	9	102.4	4th	5th	Aerobic, non-hemolytic streptococci Aerobic, non-hemolytic diphtheroid
S59	B.	13	1½	0	0	I°	3	101.6	4th	5th	Aerobic non-hemolytic stretococci Aerobic non-hemolytic diphtheroid
S32	B.	18	1½	0	28	II°	5	100.6	4th	5th	Aerobic non-hemolytic streptococci Anaerobic non-hemolytic diphtheroid *Staph. albus*
S54	B.	24	1	0	0	II°	3	103.6	3d	4th	Aerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S16	W.	6½	3	0	0	I°	4	103.8	4th	4th	Anaerobic, alpha-viridans streptococci Aerobic, non-hemolytic diphtheroid *Staph. albus*
S77	B.	13	1	1	0	I°	4	101	4th	5th	Anaerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S98	B.	12	½	0	0	I°	6	101	2d	5th	Anaerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S110	W.	12	1	0	0	I°	3	102.6	2d	3d	Anaerobic, non-hemolytic streptococci Aerobic, non-hemolytic diphtheroid
S112	B.	10	½	2	0	I°	4	101	5th	5th	Anaerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S24	B.	4	1½	1	0	II°	28	101.6	5th	5th	Anaerobic, non-hemolytic streptococci *Staph. albus*
S25	B.	20	½	1	0	II°	3	101.2	4th	4th	Anaerobic, non-hemolytic streptococci *B. coli communis* Anaerobic, non-hemolytic diphtheroid

TABLE IV—*Continued*

BACTERIOLOGICAL NUMBER	RACE	DURATION OF LABOR		VAGINAL EXAMINATION	PREMATURE RUPTURE OF MEMBRANES	PERINEAL TEARS	PUERPERIUM				UTERINE CULTURE
		Total	Second stage				Duration of fever	Highest temperature	Day of highest temperature	Day of culture	
		hours	*hours*		*hours*		*days*				
S30	B.	30	1	0	0	I°	3	100.6	3d	4th	Anaerobic, non-hemolytic streptococci *B. coli communis* Anaerobic non-hemolytic diphtheroid
S60	B.	28	1	1	0	I°	9	104.8	7th	5th	Anaerobic, non-hemolytic streptococci Aerobic, non-hemolytic diphtheroid
S66	B.	10	2	0	0	I°	6	101	3d	4th	Anaerobic, non-hemolytic streptococci *B. pseudonecrophorus* Anaerobic, non-hemolytic diphtheroid
S78	B.	53	1½	0	8	0	4	102	3d	4th	Anaerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S117	B.	5	2	1	5	0	4	102.8	6th	5th	Anaerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S18	B.	2	1	0	0	I°	4	101	5th	6th	Anaerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S23	B.	16	½	0	2	I°	8	103.2	5th	3d	Anaerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S26	B.	10	1	0	0	I°	4	101.2	4th	5th	Anaerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S39	B.	21	1	0	0	I°	5	101.6	6th	5th	Anaerobic, non-hemolytic streptococci *Staph. albus*

S49	B.	25½	½	0	25	II°	7	102	4th	5th	Anaerobic, non-hemolytic streptococci Aerobic, non-hemolytic diphtheroid
S56	B.	63	1	0	0	I°	4	102	5th	5th	Anaerobic, non-hemolytic streptococci Aerobic, non-hemolytic diphtheroid
S62	W.	12½	1	0	0	I°	4	102.2	2d	3d	Anaerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S87	B.	8	½	0	0	I°	6	101.8	5th	3d	Anaerobic, non-hemolytic streptococci Aerobic, non-hemolytic diphtheroid
S93	B.	30	2	0	0	I°	5	101.4	3d	4th	Anaerobic, non-hemolytic streptococci Aerobic, non-hemolytic diphtheroid
S102	W.	10	½	0	0	I°	6	101.2	5th	5th	Anaerobic, non-hemolytic streptococci *Staph. albus*
S103	B.	18	2	0	0	II°	6	101.4	4th	5th	Anaerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S108	W.	18	1	0	3	I°	3	100.6	2d	4th	Anaerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S3	W.	17	3	0	17	0	23	102	12th	6th	Aerobic, alpha-viridans streptococci
S97	W	11	1	0	10	0	5	102	4th	5th	Aerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid *Staph. albus*
S46	B.	9	1	0	9	0	9	103	4th	5th	Aerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S8	W.	65	2	0	38	0	8	101.8	3d	3d	Aerobic, non-hemolytic streptococci *B. coli communis* Aerobic, non-hemolytic diphtheroid

TABLE V

Clinical data and bacteriological findings in 25 patients infected following spontaneous delivery, but in whom no vaginal examinations had been made, and in whom premature rupture of the membranes or perineal tear had not occurred

BACTERIOLOGICAL NUMBER	RACE	DURATION OF LABOR		PUERPERIUM				UTERINE CULTURE
		Total	Second stage	Duration of fever	Highest temperature	Day of highest temperature	Day of culture	
		hours	*hours*	*days*				
S90	W.	7	½	5	103.8	2d	3d	Aerobic, beta-hemolytic streptococci
S17	B.	17	1	5	103.6	5th	5th	Aerobic, alpha-viridans streptococci *B. pseudonecrophorus. B. coli communis* Aerobic, non-hemolytic diphtheroid
S57	B.	15	½	8	105	6th	5th	Aerobic, alpha-viridans streptococci Aerobic, non-hemolytic diphtheroid
S12	B.	14	1	6	101.4	6th	5th	Aerobic, alpha-viridans streptococci
S80	B.	32	½	12	103.6	7th	6th	Aerobic, alpha-viridans streptococci Anaerobic, non-hemolytic diphtheroid
S94	W.	23	1	17	105.2	6th	5th	Aerobic, non-hemolytic streptococci *Staph. albus*
S48	B.	19	1	4	102	4th	5th	Aerobic, non-hemolytic streptococci Aerobic, non-hemolytic diphtheroid
S92	B.	10	½	7	101.6	5th	4th	Aerobic, non-hemolytic streptococci Aerobic, non-hemolytic diphtheroid
S106	B.	5	1	6	101.4	4th	5th	Aerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S79	B.	21	1	6	102.2	3d	3d	Anaerobic, beta-hemolytic streptococci *B. coli communis. Staph. albus*
S50	B.	6½	½	8	101.8	3d	4th	Anaerobic, alpha-viridans streptococci *B. pseudonecrophorus* Aerobic, non-hemolytic diphtheroid
S74	B.	14	1	5	101.4	3d	4th	Anaerobic, non-hemolytic streptococci Aerobic, non-hemolytic diphtheroid
S65	B.	14	½	4	101.2	3d	5th	Anaerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid

TABLE V—*Continued*

BACTERIOLOGICAL NUMBER	RACE	DURATION OF LABOR		PUERPERIUM				UTERINE CULTURE
		Total	Second stage	Duration of fever	Highest temperature	Day of highest temperature	Day of culture	
		hours	*hours*	*days*				
S22	B.	7	½	3	104	4th	5th	Anaerobic, non-hemolytic streptococci *B. coli communis* Aerobic, non-hemolytic diphtheroid
S53	B.	21	½	5	103	3d	5th	Anaerobic, non-hemolytic streptococci Aerobic, non-hemolytic diphtheroid *Staph. albus*
S64	W.	12	½	5	102.4	3d	4th	Anaerobic, non-hemolytic streptococci Aerobic, non-hemolytic diphtheroid
S107	B.	8	½	4	102	4th	5th	Anaerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S28	B.	10	½	3	102.2	2d	3d	Anaerobic, non-hemolytic streptococci *B. coli communis* Anaerobic, non-hemolytic diphtheroid
S44	B.	11½	½	3	102	4th	5th	Anaerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S45	B.	15½	½	7	101.6	6th	5th	Anaerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S68	B.	24½	½	6	102.8	4th	5th	Anaerobic, non-hemolytic streptococci Aerobic, non-hemolytic diphtheroid
S71	B.	7½	2	3	101	3d	4th	Anaerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid *Staph. albus*
S73	W.	7½	1	3	101	3d	4th	Anaerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S88	W.	8½	1	5	102.4	2d	4th	Anaerobic, non-hemolytic streptococci Anaerobic, non-hemolytic diphtheroid
S111	B.	6	½	3	101.4	2d	3d	Anaerobic, non-hemolyic streptococci Aerobic, non-hemolytic diphtheroid *Staph. albus*

normal was premature rupture of the membranes. None of the patients in this series were seriously ill and all recovered without extension of the infection beyond the uterus. Aerobic, beta-hemolytic streptococci were the infecting organisms in six of the forty-two patients, an incidence of 14 per cent.

Table V presents the data from 25 patients who were delivered spontaneously at term without vaginal examinations during the course of labor, without premature rupture of the membranes and without perineal lacerations. In only one of them was the aerobic, beta-hemolytic streptococcus the infecting organism, an incidence of 4 per cent. In this group, likewise, all of the patients recovered without extension of the infectious process beyond the uterus. None was seriously ill and in only one patient did the fever last longer than two weeks.

DISCUSSION

It seems to us that the cases we have presented may be studied with profit from two points of view. It is generally admitted that various strains of aerobic, beta-hemolytic streptococci are usually those of most serious import in puerperal infection. We shall, therefore, attempt to trace the origin of these organisms in our cases. Moreover, it might prove of interest to study our cases from the viewpoint of racial incidence.

Puerperal infection due to aerobic, beta-hemolytic streptococci

Of the 116 strains of streptococci isolated from 113 patients, 24 were of the aerobic, beta-hemolytic variety. The first five tables show that they were distributed as follows:

11	Abortions	beta-hem. strep. 7, or 63%
28	Operative deliveries	beta-hem. strep. 7, or 25%
7	Spontaneous deliveries with various puerperal complications	beta-hem. strep. 3, or 43%
42	Spontaneous deliveries with vaginal examinations, perineal tears, or premature rupture of the membranes	beta-hem. strep. 6, or 14%
25	Spontaneous deliveries without the above	beta-hem. strep. 1, or 4%
113	Total	beta-hem. strep. 24

In other words, our observations seem to show that puerperal infection due to aerobic, beta-hemolytic streptococci is exogenous in origin,

the organism except in rare instances being introduced into the birth canal at the time of labor or shortly thereafter, and rarely occurs when a proper technique is employed and all possibility for external infection is avoided. There is still a considerable divergence of opinion as to whether or not normal pregnant women harbor aerobic, beta-hemolytic streptococci in the vagina and cervix. It seems to us that this needs further careful investigation. Our own work does not throw direct light on this point. However, the following observation may be of indirect value. We have recently made a bacteriological study of the flora of the vagina in a series of thirty afebrile women on the fifth day of the puerperium, none of whom showed signs of infection. While streptococci were isolated in twenty-four of the cases studied, in no instance were they of the aerobic, beta-hemolytic variety. Of course, such a series is too small to permit definite conclusions but, should the same findings obtain in a larger series, it would be difficult to imagine that aerobic, beta-hemolytic streptococci could have been present during pregnancy but had disappeared by the fifth day of the puerperium. Moreover, it seems to us that the fact that aerobic, beta-hemolytic streptococci were found in only one of twenty-five patients delivered spontaneously without premature rupture of the membranes, vaginal examinations or perineal lacerations, as shown in Table V, is good evidence that this type of infection, which is generally admitted to have the most serious prognosis, is in most instances introduced from the outside at the time of labor or early in the puerperium. In other words, the responsibility for puerperal infection due to aerobic, beta-hemolytic streptococci must rest largely on the attendants at the time of labor. Since this is the type of infection which is, in great part, responsible for the high maternal mortality in puerperal infection, it seems to us that our figures reinforce the plea for more conservative obstetrics and, particularly, for the necessity for the limitation of unnecessary vaginal examination and operative interference at the time of labor.

As to the source of the gamma, non-hemolytic streptococci, we believe there is sufficient evidence to warrant the statement that these organisms are frequently harbored in the vagina and cervix of normal non-pregnant, pregnant, parturient and puerperal women. If such

is the case, it is probable that their upward extension into the uterus must occur in a number of cases at the time of labor.

Racial incidence of streptococcic puerperal infection

When our 102 cases of streptococcic puerperal infection occurring in women delivered at term are studied from the point of view of racial incidence, several points of interest can be noted. In our series there were 27 whites and 75 black patients. In other words, streptococcic puerperal infection occurred approximately three times more often in the blacks than in the whites. This difference cannot be explained on the basis of any difference in the racial census of our service, since the two races are approximately equally represented in our wards. Moreover, this racial difference in regard to the incidence of infection is further emphasized by some, as yet, unpublished statistics collected by Dr. Williams. He found that in the last five thousand deliveries in the Johns Hopkins Hospital, ending November 1, 1927, the incidence of puerperal infection was approximately twice as great among the blacks as among the whites. This applied to the series as a whole, as well as to the patients who were delivered spontaneously without vaginal examinations and without perineal lacerations.

From the 102 patients delivered at term we recovered and studied 103 strains of streptococci. The racial incidence of the various types of the organism is shown below:

	WHITE	BLACK
Aerobic		
Beta	7	10
Alpha	0	1
Alpha viridans	5	7
Gamma	4	15
Anaerobic		
Alpha viridans	3	2
Viridans (non-hemolytic)	0	1
Gamma	8	40
Total	27	76

Our figures show that there is no marked difference in the racial incidence of the various types of streptococci except in the case of the

gamma, non-hemolytic variety. That aerobic, beta-hemolytic streptococci occur with relatively equal frequency in the two races is, we believe, additional evidence that that type of infection is exogenous in character.

Our work shows that in our material gamma, non-hemolytic, streptococcic puerperal infection occurred approximately five times as frequently in the blacks as in the whites,—a fact that demands explanation. We believe that it is this type of streptococcus which gives rise to the preponderance of puerperal infection of the black race. Moreover, if this type of streptococcus is frequently harbored in the vagina and cervix during pregnancy, one might expect it to occur more frequently in the black than in the white, as the result of the lack of cleanliness in the former. This may possibly be the explanation. On the other hand, we have recently cultured the vaginae of thirty normal, non-infected women on the fifth day of the puerperium—15 whites and 15 blacks. In twenty-four instances streptococci were recovered —three aerobic, alpha-hemolytic; four aerobic, gamma, non-hemolytic; seventeen anaerobic, gamma, non-hemolytic—and the two races were equally represented. Of course, this series is much too small to be conclusive and the same proportion might not obtain in a more extensive study.

It seems to us that another factor must be considered. It is generally recognized that the black woman living in a city, usually under very defective hygienic conditions, is a poor physical specimen, and is prone to infections of all kinds. In other words, the whole question of immunity and resistance must be considered, and it is probable that such factors are not so well developed in the black as in the white race.

In spite of certain work to the contrary, we have not been able to convince ourselves that streptococci can exist in the early puerperal uterus for any length of time without giving rise to clinical manifestations of infection, except in the rarest instances. In *The Bulletin of the Johns Hopkins Hospital* for July, 1928 there appeared a report by us of the results of cultures of thirty uteri in normal, non-infected women on the fifth day of the puerperium. While only ten of the thirty uteri were sterile, none contained streptococci. If streptococci are harbored in the vagina and cervix during pregnancy they in all probability would

ascend into the uterus during labor. They may be killed off rapidly in patients whose powers of resistance are well developed, while in those with lesser resistance the streptococci may remain alive and give rise to infection. The difference in the incidence of puerperal infection due to gamma, non-hemolytic streptococci, which we have shown to exist in the two races, possibly may be explained on this basis.

BACTERIOLOGY

Methods

The agar, broth and gelatin used were meat (usually pork) infusion media with a reaction of about pH 7.6. In making blood agar plates about 0.75 cc. of defibrinated human blood was added to about 12 cc. of agar which had been melted and cooled to 45° to 50°C. "Pour" plates were always made and the type of appearance in blood agar was always determined by the microscopic study of deep colonies after incubation for 48 hours and again after refrigeration for 24 or 48 hours. Anaerobic plates and tubes were incubated in the jar described by one of us (2).

Fermentation reactions were determined in fermented broth prepared by the method of Smith (3). The carbohydrates were autoclaved in 10 per cent aqueous solution and then added aseptically to the broth in sufficient amount to make concentrations of one per cent of the test substance in the medium. To promote abundant growth there were added aseptically to each tube of broth five drops of human serum, previously heated to destroy the saccharolytic enzymes (Ten-Broeck (4)). After incubation of the cultures in the test media for one week, hydrogen-ion concentrations were determined by the method of Brown (5).

All strains were grown in plain and peptone milk. The results were the same in these two media. Gelatin cultures were incubated at 37°C. for one week and then refrigerated to determine whether or not liquefaction had taken place. Gas produced in cooked meat was manifested by the raising of the vaseline plug. Mice were injected intraperitoneally with 0.5 cc. of a 24- or 48-hour broth culture. In all cases either death occurred within 24 hours, or the mice survived.

Results

The streptococci found may be summarized with reference to type in blood agar and relation to oxygen as follows:

TYPE IN BLOOD AGAR	AEROBIC	ANAEROBIC	TOTAL
Beta	24	2	26
Alpha	14	6	20
Gamma	21	49	70
Total	59	57	116

From these figures it is seen that aerobic and anaerobic strains of streptococci were found in about equal numbers. Alpha, beta and gamma types in blood agar were found among both aerobic and anaerobic strains, but there is a very great difference in their relative numbers. Beta strains were the most numerous among the aerobic streptococci, whereas 49 of the 57 anaerobic streptococci were of the gamma type. Considering both aerobic and anaerobic groups together, 70 of the 116 strains, or 60 per cent, were of the gamma type.

The characters of the individual strains are detailed in Tables VI and VII. A number of striking features are worthy of comment. Foremost is the existence of a large number of strains—thirty-one in all—which do not ferment any of the carbohydrates. Since such streptococci were not included in Brown's (6) tabulation we have given them the designation 0.0 in the tables. These were distributed among the various groups as follows:

Non-fermentative streptococci

TYPE IN BLOOD AGAR	AEROBIC	ANAEROBIC	TOTAL
Beta	0	1	1
Alpha	2	1	3
Gamma	6	21	27
Total	8	23	31

It is seen that most of the non-fermentative streptococci found in this study belong to the anaerobic gamma type.

TABLE VI

Cultural and biological characters of the aerobic streptococci

CASE NUMBER	RELATION TO OXYGEN	TYPE IN BLOOD AGAR	FERMENTATION REACTIONS								MILK COAGULATED	COOKED MEAT, GAS	GELATIN LIQUID	MOUSE PATHOGENICITY	NOMENCLATURE (HOLMAN 7)	DESIGNATION (BROWN 6)
			Glucose	Maltose	Sucrose	Lactose	Raffinose	Inulin	Mannite	Salicin						
S55	Aerobic	Beta	4.8	4.8	5.1	5.2	5.6	7.0	5.1	4.8	+	−	+	−	*S. infrequens*	Aerobic β 5.2
S75	Aerobic	Beta	4.8	4.8	5.0	5.0	4.9	7.0	5.0	4.8	+	−	−	−	*S. infrequens*	Aerobic β 5.2
S91	Aerobic	Beta	4.9	4.9	4.9	4.9	4.9	6.8	6.8	5.0	+	−	−	+	*S. pyogenes*	Aerobic β 1.2
S119	Aerobic	Beta	4.8	4.8	4.8	4.9	5.0	7.1	7.2	5.1	+	−	−	−	*S. pyogenes*	Aerobic β 1.2
S89	Aerobic	Beta	5.1	5.1	5.1	5.1	3.3	6.8	6.9	5.3	+	−	−	−	*S. pyogenes*	Aerobic β 1.2
S85	Aerobic	Beta	4.8	4.8	4.8	4.8	4.8	7.2	7.1	4.8	+	−	−	−	*S. pyogenes*	Aerobic β 1.2
S11 B	Aerobic	Beta	4.8	4.8	4.8	4.8	4.8	6.7	6.7	5.3	+	−	−	−	*S. pyogenes*	Aerobic β 1.2
S58	Aerobic	Beta	4.8	4.8	4.8	4.9	4.9	7.0	7.0	4.8	+	−	−	−	*S. pyogenes*	Aerobic β 1.2
S47	Aerobic	Beta	5.0	5.1	5.0	5.3	7.4	7.6	7.4	5.5	+	−	+	+	*S. pyogenes*	Aerobic β 1.1
S42	Aerobic	Beta	4.8	5.1	5.2	5.1	7.3	7.3	7.4	5.3	+	−	+	+	*S. pyogenes*	Aerobic β 1.1
S33	Aerobic	Beta	5.1	5.1	5.3	5.3	7.2	7.4	7.4	5.3	+	−	−	+	*S. pyogenes*	Aerobic β 1.1
S34	Aerobic	Beta	5.0	5.1	5.3	5.2	7.0	7.4	7.4	5.3	+	−	−	+	*S. pyogenes*	Aerobic β 1.1
S40	Aerobic	Beta	5.0	5.1	5.1	5.4	7.3	7.4	7.3	5.2	+	−	−	+	*S. pyogenes*	Aerobic β 1.1
S72	Aerobic	Beta	4.9	5.1	5.1	5.4	7.0	7.0	7.0	5.4	+	−	−	+	*S. pyogenes*	Aerobic β 1.1
S76	Aerobic	Beta	5.0	5.0	5.0	5.2	6.9	7.0	7.1	5.3	+	−	−	+	*S. pyogenes*	Aerobic β 1.1
S6	Aerobic	Beta	5.3	5.3	5.2	5.4	7.1	7.2	7.1	5.4	+	−	−	−	*S. pyogenes*	Aerobic β 1.1
S90	Aerobic	Beta	5.0	5.1	5.1	5.1	7.0	7.0	7.0	5.1	+	−	−	+	*S. pyogenes*	Aerobic β 1.1
S115	Aerobic	Beta	5.1	5.2	5.3	5.5	6.9	7.0	7.2	5.4	+	−	−	+	*S. pyogenes*	Aerobic β 1.1
S96	Aerobic	Beta	5.0	5.0	5.0	5.4	6.8	6.8	6.8	5.6	+	−	−	+	*S. pyogenes*	Aerobic β 1.1
S84	Aerobic	Beta	4.8	5.1	6.1	5.3	7.0	7.0	7.0	5.3	+	−	−	+	*S. pyogenes*	Aerobic β 1.1
S86	Aerobic	Beta	4.8	5.0	4.9	6.9	6.8	6.8	6.9	5.1	−	−	−	+	*S. equi*	Aerobic β 3.1
S31	Aerobic	Beta	5.2	5.3	5.4	6.8	7.2	7.2	7.0	7.1	−	+	+	−	*S. subacidus*	Aerobic β 4.1
S95	Aerobic	Beta	5.2	5.8	6.9	6.9	7.0	7.0	7.0	7.1	−	−	+	−	*S. subacidus*	Aerobic β 4.5
S109	Aerobic	Beta	5.9	5.9	7.4	7.4	7.5	7.4	7.5	7.5	−	−	−	−	*S. subacidus*	Aerobic β 4.5
S43	Aerobic	Alpha prime	5.1	5.0	5.1	5.2	5.6	7.0	7.1	5.3	+	−	+	−		Aerobic α 1.2
S17	Aerobic	Alpha (viridans)	4.8	4.8	4.8	4.8	4.9	7.7	5.1	5.1	+	+	−	−	*S. fecalis*	Aerobic α 5.2
S69	Aerobic	Alpha (viridans)	4.8	4.8	4.8	4.8	4.8	6.8	7.0	4.9	+	−	−	+	*S. mitis*	Aerobic α 1.2

S15	Aerobic	Alpha (viridans)	5.4	5.4	5.4	5.8	5.5	6.9	6.9	5.8	+	−	−	−	*S. mitis*	Aerobic α 1.2
S11 A	Aerobic	Alpha (viridans)	4.8	4.8	4.8	4.8	4.8	6.7	7.0	5.1	+	−	−	−	*S. mitis*	Aerobic α 1.2
S14	Aerobic	Alpha (viridans)	4.8	4.8	4.8	4.8	4.8	7.3	7.5	4.8	+	−	−	−	*S. mitis*	Aerobic α 1.2
S82	Aerobic	Alpha (viridans)	4.8	4.8	4.8	4.8	4.8	7.0	7.0	6.9	+	−	−	+	*S. salivarius*	Aerobic α 2.2
S52	Aerobic	Alpha (viridans)	5.5	5.6	5.7	5.8	7.0	7.4	7.6	7.4	+	−	−	−	*S. salivarius*	Aerobic α 2.1
S57	Aerobic	Alpha (viridans)	5.3	5.4	5.3	7.3	7.8	7.8	7.8	7.8	−	−	+	−	*S. ignavus*	Aerobic α 4.1
S51	Aerobic	Alpha (viridans)	5.4	6.0	*6.6*	7.4	7.0	7.0	7.4	*6.4*	−	+	−	−	*S. ignavus*	Aerobic α 4.5 or 3.1
S3	Aerobic	Alpha (viridans)	5.2	*6.7*	5.2	7.3	7.3	7.3	7.3	7.3	−	−	−	−	*S. ignavus*	Aerobic α 4.1
S12	Aerobic	Alpha (viridans)	5.8	5.9	6.7	6.7	6.7	6.7	6.7	6.9	−	−	−	−	*S. ignavus*	Aerobic α 4.5
S9	Aerobic	Alpha (viridans)	*6.7*	*6.6*	6.9	6.9	7.0	6.9	7.1	7.0	−	−	−	−		Aerobic α 0.0
S80	Aerobic	Alpha (viridans)	6.9	7.2	7.0	6.9	7.1	7.1	7.3	7.2	−	−	−	−		Aerobic α 0.0
S1	Aerobic	Gamma	4.8	4.8	5.0	5.0	5.2	5.6	5.0	5.2	+	+	+	−	*S. fecalis*	Aerobic γ 5.4
S105	Aerobic	Gamma	4.8	4.8	5.6	5.1	5.1	6.9	5.2	4.8	+	−	+	−	*S. fecalis*	Aerobic γ 5.2
S36	Aerobic	Gamma	4.8	4.8	5.0	4.9	4.9	6.9	5.2	4.8	+	−	−	+	*S. fecalis*	Aerobic γ 5.2
S94	Aerobic	Gamma	4.8	4.8	4.8	4.9	4.8	7.2	4.8	4.8	+	−	−	−	*S. fecalis*	Aerobic γ 5.2
S41 B	Aerobic	Gamma	4.8	4.8	5.0	5.0	4.8	7.4	5.0	4.8	+	−	−	−	*S. fecalis*	Aerobic γ 5.2
S4	Aerobic	Gamma	4.8	4.8	4.8	4.8	4.8	7.3	5.0	5.4	+	−	−	−	*S. fecalis*	Aerobic γ 5.2
S2	Aerobic	Gamma	5.0	5.0	5.1	5.1	5.0	7.2	5.2	5.4	+	−	−	−	*S. fecalis*	Aerobic γ 5.2
S104	Aerobic	Gamma	5.0	5.1	5.1	5.2	5.1	6.8	6.9	5.4	+	−	+	−	*S. mitis*	Aerobic γ 1.2
S7	Aerobic	Gamma	4.8	4.8	4.8	4.9	5.3	7.4	7.5	5.1	+	−	−	−	*S. mitis*	Aerobic γ 1.2
S61	Aerobic	Gamma	5.3	5.5	5.4	5.3	7.5	7.4	7.3	5.4	+	−	+	+	*S. mitis*	Aerobic γ 1.1
S48	Aerobic	Gamma	4.8	4.8	4.8	4.9	7.1	7.2	7.1	4.9	+	−	−	−	*S. mitis*	Aerobic γ 1.1
S97	Aerobic	Gamma	5.2	5.1	5.1	7.1	7.1	7.0	7.2	5.1	−	+	+	−	*S. equinus*	Aerobic γ 3.1
S46	Aerobic	Gamma	6.0	6.1	6.1	7.3	7.4	7.5	7.3	6.2	−	−	−	−	*S. equinus*	Aerobic γ 3.1
S59	Aerobic	Gamma	5.4	5.5	5.5	7.6	7.3	7.5	7.6	7.5	−	−	−	−	*S. ignavus*	Aerobic γ 4.1
S27	Aerobic	Gamma	4.8	5.0	7.4	6.2	7.0	7.6	7.3	7.2	+	+	+	−	*S. salivarius*	Aerobic γ 2.5
S29	Aerobic	Gamma	7.3	7.2	7.2	7.2	7.2	7.3	7.3	7.1	−	−	+	−		Aerobic γ 0.0
S106	Aerobic	Gamma	7.6	7.3	7.4	7.4	7.5	7.4	7.3	7.3	−	+	−	−		Aerobic γ 0.0
S32	Aerobic	Gamma	7.0	7.1	7.3	7.2	7.1	7.0	7.1	7.1	−	−	−	−		Aerobic γ 0.0
S8	Aerobic	Gamma	7.5	7.4	7.6	7.5	7.6	7.6	7.6	7.6	−	−	−	−		Aerobic γ 0.0
S54	Aerobic	Gamma	7.1	7.4	7.6	7.5	7.8	7.8	7.8	7.8	−	−	−	−		Aerobic γ 0.0
S92	Aerobic	Gamma	7.3	7.1	7.3	7.3	7.3	7.3	7.3	7.3	−	−	−	−		Aerobic γ 0.0

See note at bottom of Table VII.

TABLE VII

Cultural and biological characters of the anaerobic streptococci

CASE NUMBER	RELATION TO OXYGEN	TYPE IN BLOOD AGAR	FERMENTATION REACTIONS								MILK COAGULATED	COOKED MEAT, GAS	GELATIN LIQUID	MOUSE PATHOGENICITY	NOMENCLATURE (PREVOT 8)	DESIGNATION (BROWN 6)
			Glucose	Maltose	Sucrose	Lactose	Raffinose	Inulin	Mannite	Salicin						
S113	Anaerobic	Beta	5.5	5.7	6.0	6.5	7.0	7.0	7.0	6.9	−	+	−	−	Group A1	Anaerobic β 4.1
S79	Anaerobic	Beta	7.1	7.6	7.6	7.6	7.4	7.4	7.6	7.6	−	−	−	−	*S. micros*	Anaerobic β 0.0
S63 B	Anaerobic	Alpha (viridans)	5.4	5.6	7.6	6.0	7.6	7.6	7.7	7.3	+	+	−	−		Anaerobic α 2.5
S16	Anaerobic	Alpha (viridans)	5.3	5.5	5.3	7.5	7.6	7.5	7.4	7.4	−	+	−	−	Group A1	Anaerobic α 4.1
S20	Anaerobic	Alpha (viridans)	4.8	5.0	4.8	7.3	7.4	7.4	7.2	7.2	−	+	−	−	Group A1	Anaerobic α 4.1
S41 A	Anaerobic	Alpha (viridans)	5.3	6.3	6.8	7.1	6.9	7.0	7.1	7.0	−	+	−	−	Group A1	Anaerobic α 4.5
S50	Anaerobic	Alpha (viridans)	7.6	7.8	7.8	7.8	7.8	7.8	7.7	7.4	−	−	−	−	*S. micros*	Anaerobic α 0.0
S81	Anaerobic	Viridans	5.3	5.7	6.8	7.0	7.0	7.0	7.0	7.0	−	+	−	−	Group A1	Anaerobic Δ 4.5
S77	Anaerobic	Gamma	4.8	4.9	4.8	4.8	4.8	7.2	5.0	4.8	+	−	−	−	*S. intermedius*	Anaerobic γ5.2
S74	Anaerobic	Gamma	4.8	4.8	4.8	4.8	5.1	7.2	7.0	5.1	+	−	−	−	*S. intermedius*	Anaerobic γ 1.2
S24	Anaerobic	Gamma	6.0	6.0	6.2	6.2	7.7	7.7	7.6	7.6	+	+	−	−		Anaerobic γ 2.1
S65	Anaerobic	Gamma	5.4	5.6	5.6	6.4	7.0	7.0	7.0	5.9	−	+	−	−	Group A1	Anaerobic γ 1.1 or 3.1
S99	Anaerobic	Gamma	5.4	5.4	5.4	6.9	7.4	7.4	7.2	5.5	−	+	+	−		Anaerobic γ 3.1
S118	Anaerobic	Gamma	5.0	5.5	5.5	7.9	7.1	7.9	7.9	5.5	−	+	−	−	Group A1	Anaerobic γ 3.1
S120	Anaerobic	Gamma	4.9	5.2	5.0	7.0	6.9	6.9	6.9	5.5	−	+	−	−	Group A1	Anaerobic γ 3.1
S38	Anaerobic	Gamma	5.3	5.3	6.8	5.3	7.0	7.1	7.0	6.9	+	+	−	−		Anaerobic γ 2.5
S107	Anaerobic	Gamma	4.9	5.0	6.8	6.3	7.1	7.1	7.2	7.2	−	−	−	−	*S. micros*	Anaerobic γ 2.5
S21	Anaerobic	Gamma	5.5	6.0	5.6	7.7	7.0	7.6	7.6	7.6	−	+	−	−	Group A1	Anaerobic γ 4.1
S98	Anaerobic	Gamma	5.4	5.5	5.4	7.1	7.0	7.0	7.0	7.1	−	+	−	−	Group A1	Anaerobic γ 4.1
S110	Anaerobic	Gamma	5.2	5.8	5.1	7.3	7.6	7.4	7.6	7.5	−	+	−	−	Group A1	Anaerobic γ 4.1

S112	Anaerobic	Gamma	5.5	5.7	5.8	7.5	7.5	7.5	7.5	7.5	−	−	−	−	*S. micros*	Anaerobic γ 4.1
S83	Anaerobic	Gamma	5.3	5.8	5.6	6.9	7.5	7.5	7.5	7.6	−	−	−	−	*S. micros*	Anaerobic γ 4.1
S30	Anaerobic	Gamma	5.3	5.5	7.0	7.0	7.0	7.1	7.2	7.0	−	+	−	−	Group A1	Anaerobic γ 4.5
S117	Anaerobic	Gamma	5.5	5.6	6.9	6.8	7.1	7.1	6.9	6.9	−	+	−	−	Group A1	Anaerobic γ 4.5
S53	Anaerobic	Gamma	5.5	5.6	7.0	7.0	7.0	7.0	7.0	7.0	−	+	−	−	Group A1	Anaerobic γ 4.5
S60	Anaerobic	Gamma	5.6	5.7	7.0	7.1	7.2	7.1	7.1	7.2	−	+	−	−	Group A1	Anaerobic γ 4.5
S64	Anaerobic	Gamma	5.2	5.5	6.8	7.0	6.9	6.9	6.8	7.0	−	+	−	−	Group A1	Anaerobic γ 4.5
S66	Anaerobic	Gamma	5.5	5.7	7.0	7.0	7.0	7.0	7.0	7.0	−	+	−	−	Group A1	Anaerobic γ 4.5
S70	Anaerobic	Gamma	5.1	5.4	6.9	7.1	7.1	7.1	7.4	7.2	−	+	−	−	Group A1	Anaerobic γ 4.5
S78	Anaerobic	Gamma	5.8	5.9	7.0	7.1	7.1	7.0	7.0	7.0	−	+	−	−	Group A1	Anaerobic γ 4.5
S25	Anaerobic	Gamma	5.1	5.3	7.2	7.3	7.3	7.3	7.2	7.2	−	−	−	−	*S. micros*	Anaerobic γ 4.5
S22	Anaerobic	Gamma	5.3	5.4	7.0	7.2	7.0	7.2	7.0	7.1	−	−	−	−	*S. micros*	Anaerobic γ 4.5
S114	Anaerobic	Gamma	5.7	5.8	7.0	7.2	7.2	7.2	7.2	7.2	−	−	−	−	*S. micros*	Anaerobic γ 4.5
S28	Anaerobic	Gamma	5.8	6.6	6.9	7.0	7.0	7.1	7.6	7.0	−	−	−	−	*S. micros*	Anaerobic γ 4.5
S63 A	Anaerobic	Gamma	6.3	6.3	6.6	7.0	7.0	7.0	7.0	7.0	−	−	−	+	*S. micros*	Anaerobic γ 4.5 or 4.1
S103	Anaerobic	Gamma	6.3	6.5	7.0	7.0	7.0	7.0	6.9	7.0	−	+	−	−	Group A1	Anaerobic γ 4.5
S87	Anaerobic	Gamma	6.4	6.4	6.7	6.8	6.9	6.8	6.9	6.9	−	−	−	−	*S. micros*	Anaerobic γ 0.0 or 4.5
S108	Anaerobic	Gamma	7.1	7.0	7.2	7.0	7.3	7.1	7.2	7.3	−	+	+	−		Anaerobic γ 0.0
S111	Anaerobic	Gamma	6.9	7.0	6.9	7.2	7.2	7.3	7.2	7.4	−	−	−	+	*S. micros*	Anaerobic γ 0.0
S88	Anaerobic	Gamma	7.4	7.6	7.5	7.4	7.6	7.6	7.5	7.5	−	−	−	+	*S. micros*	Anaerobic γ 0.0
S101	Anaerobic	Gamma	7.3	7.4	7.2	7.4	7.3	7.6	7.5	7.5	−	+	−	−	Group A1	Anaerobic γ 0.0
S102	Anaerobic	Gamma	7.2	7.6	7.3	7.4	7.5	7.4	7.6	7.6	−	−	−	−	*S. micros*	Anaerobic γ 0.0
S93	Anaerobic	Gamma	7.2	7.3	7.1	7.2	7.1	7.2	7.2	7.2	−	−	−	−	*S. micros*	Anaerobic γ 0.0
S78	Anaerobic	Gamma	7.3	7.5	7.7	7.6	7.6	7.5	7.6	7.6	−	−	−	−	*S. micros*	Anaerobic γ 0.0
S71	Anaerobic	Gamma	7.7	7.7	7.7	7.7	7.7	7.6	7.5	7.4	−	−	−	−	*S. micros*	Anaerobic γ 0.0
S68	Anaerobic	Gamma	7.3	7.2	7.3	7.1	7.2	7.3	7.1	7.1	−	−	−	−	*S. micros*	Anaerobic γ 0.0
S62	Anaerobic	Gamma	7.4	7.3	7.4	7.3	7.3	7.4	7.3	7.3	−	−	−	−	*S. micros*	Anaerobic γ 0.0
S56	Anaerobic	Gamma	7.5	7.6	7.5	7.5	7.6	7.6	7.7	7.5	−	−	−	−	*S. micros*	Anaerobic γ 0.0
S49	Anaerobic	Gamma	7.3	7.3	7.3	7.3	7.4	7.4	7.3	7.4	−	−	−	−	*S. micros*	Anaerobic γ 0.0
S45	Anaerobic	Gamma	7.3	7.3	7.3	7.3	7.4	7.3	7.3	7.3	−	−	−	−	*S. micros*	Anaerobic γ 0.0

TABLE VII—*Continued*

CASE NUMBER	RELATION TO OXYGEN	TYPE IN BLOOD AGAR	FERMENTATION REACTIONS								MILK COAGULATED	COOKED MEAT. GAS	GELATIN LIQUID	MOUSE PATHOGENICITY	NOMENCLATURE (PREVOT 8)	DESIGNATION (BROWN 6)
			Glucose	Maltose	Sucrose	Lactose	Raffinose	Inulin	Mannite	Salicin						
S44	Anaerobic	Gamma	7.3	7.4	7.5	7.5	7.5	7.6	7.6	7.3	—	—	—	—	*S. micros*	Anaerobic γ 0.0
S39	Anaerobic	Gamma	7.2	7.3	7.1	7.3	7.3	7.1	7.3	7.4	—	—	—	—	*S. micros*	Anaerobic γ 0.0
S37	Anaerobic	Gamma	7.1	7.4	7.2	7.2	7.2	7.3	7.2	7.3	—	—	—	—	*S. micros*	Anaerobic γ 0.0
S35	Anaerobic	Gamma	7.1	7.1	7.4	7.3	7.1	7.2	7.2	7.2	—	—	—	—	*S. micros*	Anaerobic γ 0.0
S26	Anaerobic	Gamma	6.8	6.9	7.1	6.8	7.3	7.3	7.2	7.2	—	—	—	—	*S. micros*	Anaerobic γ 0.0
S23	Anaerobic	Gamma	7.2	7.2	7.2	7.1	7.3	7.3	7.2	7.5	—	—	—	—	*S. micros*	Anaerobic γ 0.0
S18	Anaerobic	Gamma	7.3	7.0	7.3	7.0	7.3	7.3	7.4	7.4	—	—	—	—	*S. micros*	Anaerobic γ 0.0

Note: The figures under fermentation reactions indicate pH values. The figures in bold face type are regarded as positive fermentations. Italicized figures are doubtful.

Holman (7) employed only three carbohydrates (mannite, lactose and salicin) in his classification of the aerobic streptococci and did not recognize the gamma type as distinct from the alpha type in blood agar.

Prevot (8) did not employ fermentation tests in his classification of the anaerobic streptococci. Our attempt to identify some of our strains with those described by him is based upon gas formation, coagulation of milk and liquefaction of gelatin. His Group A1 includes three species *S. foetidus*, *S. anaerobius* and *S. putridus*.

Strains which were pathogenic for mice killed the animals within 24 hours after inoculation.

One strain (S81) marked "viridans" is probably of the delta type described by Bryant (9).

The term anaerobic is only used to describe obligate anaerobes; while the term aerobic is applied to all organisms which grow aerobically. Most, if not all, of the latter are facultative organisms.

Only eleven mannite-fermenting strains were found. These were distributed as follows:

Mannite-fermenting streptococci

TYPE IN BLOOD AGAR	AEROBIC	ANAEROBIC	TOTAL
Beta	2	0	2
Alpha	1	0	1
Gamma	7	1	8
Total	10	1	11

Since mannite-fermenting streptococci are relatively common in the intestinal tract, it appears probable that very few of the streptococci found in this study are of fecal origin.

One inulin-fermenting strain was isolated, an aerobic gamma type, which fermented all the carbohydrates, liquefied gelatin, produced gas in cooked meat and was non-pathogenic for mice.

Analysis of the results obtained with lactose, sucrose, raffinose and salicin shows that the aerobic strains are much more frequently fermenters of these carbohydrates than are the anaerobic strains. Even if we eliminate from consideration the non-fermentative strains, most of which are anaerobic, and the aerobic beta strains, most of which ferment lactose, sucrose and salicin but which we suspect are of exogenous origin, and consider only the fermentative alpha and gamma strains, which with the non-fermentative strains we believe are largely endogenous or native to the vagina and cervix, we find that the anaerobic streptococci in general ferment fewer carbohydrates than do the aerobic streptococci. The final hydrogen-ion concentrations attained are about the same for anaerobic and aerobic strains; most of them lie between pH 4.8 and 5.5 agreeing in this respect with other streptococci of human origin as distinguished, for instance, from bovine streptococci which generally produce a higher acidity.

As has been previously noted for streptococci from the throat, maltose fermentation almost invariably parallels glucose fermentation and the coagulation of milk parallels the fermentation of lactose. Only 16 of the 116 strains of streptococci liquefied gelatin, and 14 of these were aerobic. On the other hand, gas formation in cooked meat medium is more commonly a function of anaerobic streptococci, 26 of

the 33 gas-producing strains being anaerobic. Pathogenicity for mice is largely limited to the aerobic, beta streptococci which ferment lactose and salicin but do not ferment mannite (*S. pyogenes*, according to Holman (7)). However, only one of the strains which fermented raffinose (beta 1.2, Brown (6)) was pathogenic for mice, whereas all but one of the group beta 1.1 (which we regard as typical *S. pyogenes*) were pathogenic.

CONCLUSIONS

Based upon our study of 113 cases of streptococcic puerperal infection the following conclusions seem justified:

1. Of all our cases of puerperal infection studied bacteriologically 67 per cent showed streptococci of various varieties in the uterine cavity.

2. Evidence is offered which seems to show that puerperal infection due to aerobic, beta-hemolytic streptococci is almost invariably exogenous in character.

3. Puerperal infection due to gamma, non-hemolytic streptococci is probably endogenous in origin in many cases, and in our series was found to occur five times more frequently in colored than in white women.

4. Aerobic and anaerobic streptococci were found with approximately equal frequency, which emphasized the necessity of anaerobic methods in suspected cases of streptococcic puerperal infection.

5. Almost one-half of the aerobic streptococci were of the beta-hemolytic variety and of these the majority belonged to the *S. pyogenes* group.

6. The majority of the anaerobic streptococci were of the gamma type in blood agar and many of them failed to ferment any of the test substances employed.

7. The relatively few mannite-fermenting streptococci in our series would seem to indicate that the streptococci causing puerperal infection are rarely of fecal origin.

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CARDIAZOL—A CLINICAL REPORT[1]

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Pentamethylenetetrazol, or Cardiazol, was introduced originally as a substitute for camphor, and is now used extensively in many clinics abroad. It apparently possesses several advantages over camphor, owing to the fact that it is water soluble, can be sterilized, keeps indefinitely, and acts very rapidly after peroral, subcutaneous, or intravenous administration.

The results of experimental work indicate that cardiazol acts mainly by stimulation of the vasomotor and respiratory center and accordingly should be of definite clinical value in the treatment of cases of circulatory collapse or in poisoning by morphine. Definite evidence of any direct action on the heart has, however, not been established.

Clinical reports are in general agreement with the experimental evidence. Ruef (1) Siebner (2) and Kaiser (3) have reported its successful use in the treatment of circulatory collapse. Dreyfus and Hanau (4) in a paper on the malaria treatment of multiple sclerosis state that they give cardiazol routinely either in the prevention or treatment of collapse during the febrile periods. Hemmerling (5) has used cardiazol instead of camphor since March, 1925, and recommends its use in cases of collapse, morphine poisoning, chronic myocardial insufficiency, cardiac asthma, and angina pectoris.

In the treatment of chronic myocardial insufficiency Fahrenkamp (6) has observed that the action on the heart exerted by strophanthin is strengthened by combination with cardiazol and is of the opinion that cardiazol inhibits the effect of strophanthin on the conduction system. He finds that smaller doses of strophanthin may be given intravenously and the danger of this method of administration much reduced when it is combined with cardiazol. Moewes (7) in discussing the use of cardiazol in the treatment of arteriosclerotic heart disease

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feels that in several of his cases its direct action on the heart strengthened the effect of digitalis which without cardiazol had proved insufficient. Cases of severe decompensation with generalized stasis were in general not affected by cardiazol alone. Pichler (8) found that cardiazol caused an increase in the systolic pressure especially in cases of arterial hypotony, and reports a very interesting case of a patient with angina pectoris whose attacks were relieved by cardiazol. In two observations on this patient he found a distinct fall in pulse

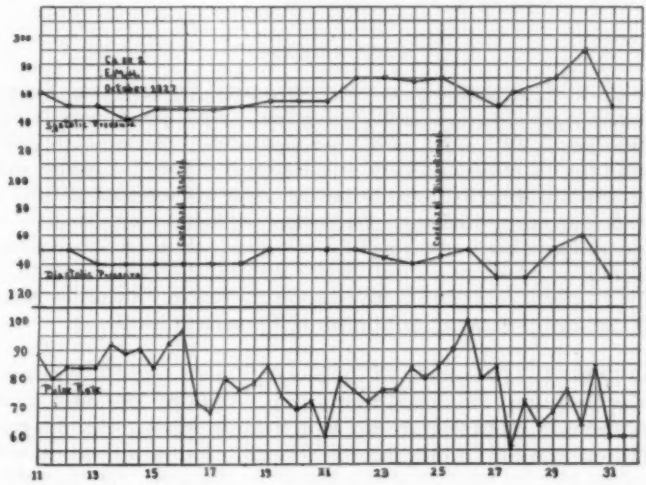

FIG. 1

rate after 0.1 gram of cardiazol perorally, and in another observation, following the administration of 0.2 gram, the pulse fell from 82 to 52 and the respirations deepened and fell from 20 to 13, without any sense of suffocation.

For the past seven months the action of cardiazol has been studied on the medical wards of the Johns Hopkins Hospital. The treatment was employed chiefly in cases of chronic myocardial insufficiency, the patients having been in the hospital for some length of time and having apparently reached a constant level of cardiac reserve as shown by clinical signs of pulmonary congestion, hepatic enlargement,

oedema, by subjective symptoms, and by measurement of fluid exchange, weight, blood pressure, and vital capacity. All patients were carefully observed for at least five days prior to the employment of cardiazol, in order to make sure that no change was taking place, and in most instances there was no change in medication other than the addition of cardiazol, during the period of observation. The chief purpose of the experiment was to determine the effect of the drug on the general course of chronic cardiovascular disease rather than its immediate effects upon the circulation.

CASE RECORDS

Case 1. R. P., an obese negress of 42. *Diagnosis*: Arteriosclerosis, hypertension, chronic nephritis, myocardial insufficiency, right bundle branch block. Admitted July 7, 1927, with marked decompensation. She responded well to treatment but the oedema gradually reaccumulated and she lost ground during August. On September 3, 10, and 19, the right chest was aspirated, 800, 950, and 650 cc. of fluid being withdrawn. On October 18, digitalis (0.1 gram) was discontinued and cardiazol substituted for nine days. A month later, cardiazol was again given, this time without varying the dose of digitalis which she had received for eleven days prior to the period of observation. On neither occasion did the cardiazol have any apparent effect on the course of the disease.

Case 2. E. M. H., a negress of 50. *Diagnosis*: Chronic nephritis, hypertension, auricular fibrillation, myocardial insufficiency. Admitted September 6, 1927. During six weeks' observation she was never free from oedema, râles were present at both lung bases and the liver remained enlarged. She was orthopnoeic and for most of the time the respirations were periodic in character. On September 12, she developed exquisite tenderness over the entire left chest, radiating up the neck and down the inner surface of the left arm. This persisted unabated. On October 16, cardiazol was started by mouth and digitalis was discontinued. Clinically, there ensued a very definite favorable change with loss of hyperesthesia and general subjective improvement. Cardiazol was discontinued on October 25. This patient finally died in uremic coma November 18. The final note by the intern is of interest. "One who saw the patient at the time of her admission with extreme myocardial insufficiency cannot help marvelling that she should have died this morning without a single sign of myocardial insufficiency. No engorgement of the veins; lungs clear at the bases; liver not palpable."

Case 3. C. S., Negress aged 22. *Diagnosis*: Rheumatic heart disease, mitral stenosis and insufficiency, myocardial insufficiency. Admitted October 7, 1927. Signs of severe congestive failure. Cardiazol was used during the first 4 days

combined with digitalis and other measures. By October 20, she was comfortable, could lie flat in bed and the physical signs of decompensation had disappeared, although the pulse rate remained very labile. On November 9, she was up for increasing periods daily and cardiazol was given as charted. In this case a very interesting effect on the pulse rate and urinary output is noted.

Case 4. A. S. L., white male, aged 60. *Diagnosis*: Hypertension; right bundle branch block; first degree heart block. This patient was sent to the hospital for a rest. He was quite comfortable in bed but became dyspnoeic on walking short distances. Cardiazol was started December 9, after 7 days' preliminary observa-

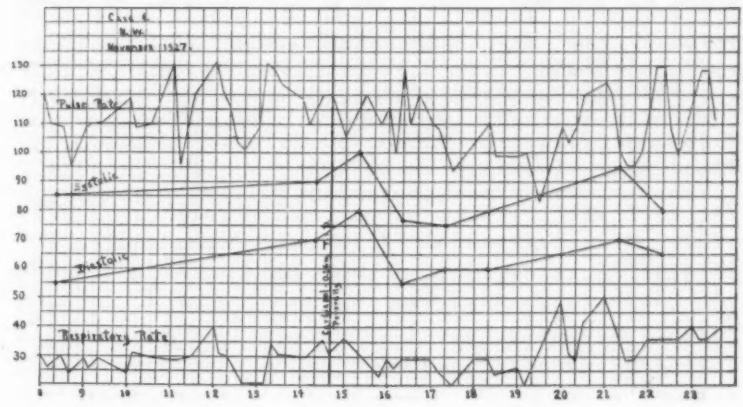

FIG. 2

tion. No effects could be noted. The patient died suddenly on December 17, possibly of cerebral hemorrhage. Autopsy not granted.

Case 5. G. S., a white male of 48. *Diagnosis*: Arteriosclerosis; hypertension; emphysema; myocardial insufficiency. Admitted December 31, 1927, with acute pulmonary oedema. Excellent response to therapy. On January 4, all medication discontinued. January 11–22, cardiazol 0.1 gram by mouth four times daily. No effect on pulse rate, blood pressure, vital capacity, or clinical condition.

Case 6. N. W., Negro 18. *Diagnosis*: Tuberculosis of lungs and peritoneum. Pleurisy with effusion. Note on November 13. "Has gone rapidly downhill, extraordinarily emaciated, almost comatose. Heart sounds much weaker. Pulse at times barely perceptible. Abdomen tense (fluid). Started cardiazol 0.1 gram by mouth every four hours. *November 14.* Today much less drowsy, in fact

quite alert. Heart sounds of better quality. Pulse much stronger. *November 16.* Is now eating quite well. Condition otherwise the same.

The patient became much worse thereafter and was discharged against advice November 22.

This case is included in the series because it shows a definite though temporary effect on blood-pressure, and clinical condition.

Case 7. G. R., white male of 49. *Diagnosis:* Chronic alcoholism; tabagism, myocardial insufficiency. Admitted November 30, 1927, and discharged February 11, 1928, unimproved. He was confined to bed during his entire stay in the hospital, was quite weak, dyspnoeic, and at night disoriented. He received

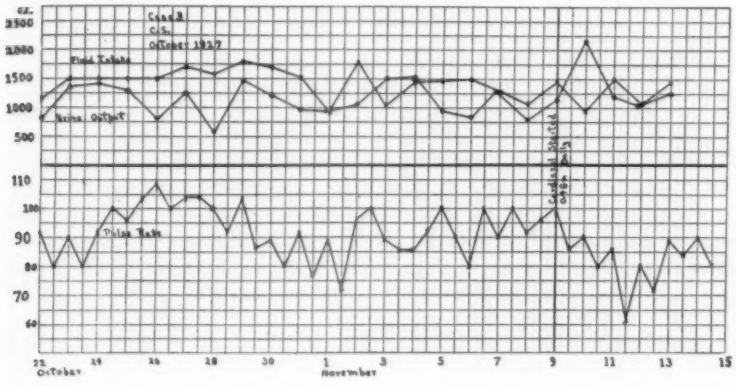

FIG. 3

cardiazol (0.1 gram) by mouth three times daily from December 23 to 30, four times daily from January 10 to 16, and 0.1 gram subcutaneously three times daily from January 30, to February 5, 1928. No effect at any time on blood pressure, pulse, vital capacity, urine output, albumin, weight, clinical or subjective condition; electrocardiogram not affected.

Case 8. P. W., negress, aged 35. *Diagnosis*: Syphilitic myocarditis; myocardial insufficiency. On admission orthopnoeic, cyanotic, respirations periodic. Observations were made of blood pressure, pulse rate and respiration every five minutes for 20 minutes; after which cardiazol (0.2 grams) was given subcutaneously and the observations were continued for 45 minutes after the injection. There were no apparent effects. On the following day a bigeminal rhythm developed, caused by ventricular premature beats. After one electrocardiographic record was taken she was given 0.2 gram of cardiazol intravenously. In the record taken

one minute after injection the heart rate had dropped from 78 to 62. Five minutes later the rate had returned to 73. Thereafter there was no significant alteration over a period of 50 minutes, records being taken at 5-minute intervals. The P-R interval increased from 0.21 to 0.22 seconds. No change in QRS complexes. The rhythm continued to vary between normal and bigeminal as it had prior to the administration ration of cardiazol.

Case 9. J. C., a negro of 47. Complete heart block. Auricular rate 78, ventricular, 37. Respirations of Cheyne-Stokes type. Blood pressure varied between 220 and 240 systolic and 110 and 126 diastolic.

Experiment. May 8, 1928. Respiration recorded continuously on kymograph. Blood-pressure determinations every 3 to 5 minutes. Electrocardiographic records every 3 to 10 minutes. Adrenalin 0.3 cc. subcutaneously. No response during 40 minutes' observation. Atropine (3 mgm.) subcutaneously—auricular rate increased from 78 to 97; ventricular rate unaltered. Slight tendency to abolition of periodic respiration for a few minutes. Dryness of mouth. Cardiazol (0.2 gram) subcutaneously. No effect noted during 40 minutes' observation of respirations and electrocardiographic records. The systolic pressure increased from 222 to 238 and the diastolic from 118 to 132.

In addition to the above cases the action of cardiazol was studied in two cases of pneumonia and in one of empyema. No effect was seen either clinically, or on daily electrocardiographic records over a period of four days' observation. In uncontrolled observations on several other patients suffering with chronic myocardial insufficiency who received cardiazol in doses of 0.1 to 0.2 gram by mouth or subcutaneously three or four times daily there was no demonstrable effect on the heart action or the peripheral circulation.

The three cases in which improvement was noted during the administration of cardiazol require further comment. In case 2 the patient had been receiving digitalis for some time and on one previous occasion had shown improvement when digitalis was stopped, so it is conceivable that the apparent effect of cardiazol was in reality due to the stopping of digitalis. Nevertheless, the fall in pulse rate and the increase in blood-pressure were both very definite. In cases 3 and 6 likewise, it is difficult to interpret the results except as an effect of cardiazol. Most striking of all, however, was the subjective improvement and the change in the general appearance of these patients.

TABLE I

CASE	CARDIASOL—DOSAGE	VITAL CAPACITY	EFFECT ON BLOOD PRESSURE	GAIN OR LOSS OF WEIGHT	URINE		EFFECT ON CLINICAL CONDITION	REMARKS
					Diuresis	Albumin		
		cc.		*pounds*				
1. R. P.	0.2 gram by mouth t.i.d. for nine days. Digitalis discontinued	1,400–900	0	−5	0	0	0	
	0.2 gram (M) t.i.d. for 15 days	700–1,000	0	+7	0	0	0	Bundle-branch block. Prolonged conduction time. No effect on electrocardiograph
2. E. M. H.	0.2 gram (M) t.i.d. for 10 days. Digitalis discontinued	1,300–1,400	+		0	0	Improvement	Effect possibly due to discontinuing digitalis.
3. C. S.	0.1 gram subcutaneously q.i.d. for three days. 0.1 gram q.i.d. for 4 days	0	0	+5½	+	0	Improvement	Diuresis. Drop in pulse rate
4. A. S. L.	0.1 gram (M) q.i.d. for nine days	0	0		0	0	0	Sudden death. (Cerebral hemorrhage?)
5. G. S.	0.1 gram (M) q.i.d. for 12 days		0	−1	0	0	0	No effect on electrocardiograph
6. N. W.	0.1 gram (M) q.i.d. for 8 days		+				Improvement	Generalized tuberculosis
7. G. R.	0.1 gram (M) t.i.d. for 8 days	0	0	0	0	0	0	
	0.1 gram (M) q.i.d. for 7 days	0	0	0	0	0	0	No effect on electrocardiograph
	0.1 gram (S) t.i.d. for 7 days	0	0	0	0	0	0	
8. P. W.	0.2 gram (S) Observation for 45 minutes (October 25)		0					No effect on blood pressure, pulse rate or respirations.
	0.2 gram Intravenously (October 26) Observation for 50 minutes							Fall in pulse rate for 5 minutes. Bigeminal rhythm unaffected
9. J. C.	0.2 gram (S) Observation for 30 minutes		+				0	Cheyne-Stokes respiration unaltered. No effect on complete heart-block

SUMMARY AND CONCLUSIONS

1. The effect of daily doses of cardiazol has been studied in cases of chronic myocardial insufficiency. No effect was seen in the majority of the patients, but three, one of which was a case of advanced tuberculosis, were apparently improved by the drug. Of these three, the blood pressure was raised in two, slowing of the pulse rate occurred in two, slight diuresis in one, and all were subjectively improved.

2. In no case was there any effect on the electrocardiographic record, either taken daily during the period of administration of the drug, or when taken at frequent intervals following the administration of a single dose.

3. No harmful effects were noted.

4. Although the chief field of usefulness for cardiazol is probably in the treatment of acute circulatory collapse, it may occasionally be used to advantage in cases of chronic myocardial insufficiency.

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A STUDY OF THE ACTION OF MERCUROCHROME, OF HORSE SERUM AND OF MIXTURES THEREOF ON PNEUMOCOCCUS INFECTIONS IN MICE[1,2]

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FOREWORD BY DR. GEORGE McCOY, HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE

It has been a pleasure to extend the facilities of the Hygienic Laboratory to Miss Justina Hill for the purpose of carrying out the experiments reported herewith. Comment on the results obtained seems hardly necessary, but the importance of this line of investigation, especially as regards the employment of mixtures of germicidal drugs with serum, appears to be strongly indicated.

With the extension of the intravenous use of mercurochrome to the treatment of infections other than those of the blood stream, or of parts of the body in which the drug is concentrated in the course of its elimination, it has become increasingly evident that the action of the drug must involve more than a direct bactericidal effect. While its direct action in strong concentrations is unquestionable, it has also been shown that dilutions of the drug, which might be present after its intravenous administration, lose much of their germicidal action in the presence of protein. This reduction of the bactericidal action of mercurochrome by protein was noted by Young, White and Swartz (1) in their original presentation of mercurochrome. They found that, while their strain of *B. coli* was killed in urine in one hour by a 1:5,000 dilution of the drug, when a parallel test was done in hydrocele fluid, a 1:1,000 dilution was required to kill in the same time. Similarly, Young, White, Hill and Davis (2), working with three strains of

[1] Received for publication October 3, 1928.

[2] Experiments performed in the Hygienic Laboratory of the United States Health Service, Washington, D. C.

B. coli, found that, while the average killing dilution of the drug in salt solution in one hour was 1:100,000 in 50 per cent dog serum a 1:500 concentration of drug was necessary to kill in the same time. So that, although it has been shown that, after the intravenous administration of the drug, the bacteriostatic action of the blood is increased from 15 to 45 minutes after injection (3) and the urine (4) and the bile (5) may be germicidal, there is no reason to expect such action in remote foci of infection. Ignoring the possibility of any but direct germicidal action, Brill and Meyers (6), Walker (7), Simmons (8) and Colebrook and Hare (9) have argued against the intravenous use of the drug. Evidence of therapeutic action under conditions in which mercurochrome was not germicidal would indicate an indirect action and would resolve some of the existing differences of opinion.

The difficulties which beset the experimental study of the action of drugs on bacterial infection are well known. It is hard to find a method in which the variables remain within the control of the experimenter, but in which the virulence is not too high, too low or too fluctuating. For this reason, the courtesy of Surgeon-General Cumming of the United States Public Health Service in making available the facilities of the Hygienic Laboratory has been greatly appreciated.

Method. Mice were inoculated and treated intraperitoneally. In most of the experiments the tests were entirely *in vivo*, that is, the animals were inoculated with 0.5 cc. of the desired culture dilution and treated at once or later. Some *in vitro-in vivo* tests were done, in which the culture dilutions and treatment substances were mixed *in vitro*, some of the combination being injected at once and some after standing at room temperature for intervals of from thirty minutes to two hours. Animals were observed for a week after inoculation. Those that died were autopsied and cultures were made from the heart blood to establish the presence of the pneumococcus. Although the high virulence of this infection discouraged the belief that any very striking results could be obtained by treatment, the method had the great advantage of varying only within reasonable limits. It must be remembered, however, that moderate differences in culture dilutions should be interpreted with some latitude, since, undoubtedly,

the virulence shifted slightly. A culture dilution of 1:20,000, for example, on one day, would be equalled, at another time, by one of 1:10,000.

Careful virulence controls were run with every test. The culture dilutions used for these controls were 1:1 million, 1:10 million, 1:100 million, and 1:1 billion. Inoculation was invariably with 0.5 cc. of the culture dilution made in broth. A summary of these controls shows that all of the 44 mice inoculated with a culture dilution of 1:1 million died, and that only one of the 44 animals receiving a culture dilution of 1:10 million survived. With a culture dilution of 1:100 million, 86.4 per cent of the 44 animals died, while with a culture dilution of 1:1 billion 75 per cent died. That is, working with culture dilutions of 1:1 million or less, death was inevitable, unless the treatment which was given influenced the infection. Early experiments, made with highly diluted cultures, showed that normal horse serum alone would protect. The strength of the dilutions were therefore increased, so that most of the experiments were performed with culture dilutions of from 1:1000 up to 1:30,000, inclusive, that is, with from 33.3 to 1000 times the invariably fatal dose.

Findings. These will be considered in the following order; first, the results with mercurochrome alone; second, the action of horse serum alone; and third, the action of mixtures of drug and serum. The tests in each of these three series are divided into two groups; first, the entirely *in vivo* tests, and second, the *in vitro-in vivo* experiments.

TREATMENT WITH MERCUROCHROME ALONE

Toxicity. It was found that normal mice tolerated relatively large intraperitoneal injections of the drug. Although the administration of 200 mgm./kgm. killed all of the four mice injected, seven of the eight mice that received 100 mgm./kgm. lived, as well as all of the eight animals given 75 mgm./kgm. One of the ten mice given 50 mgm./kgm. died on the sixth day, both of the mice given 30 mgm./kgm. surviving.

In vivo experiments. Two hundred seventy-one animals were given varying culture dilutions and different amounts of mercurochrome, treatment being instituted usually at once after inoculation, but in some cases 30 minutes, 1 or 2 hours after inoculation. The findings

with the animals which received 0.3 cc. of a 1:1000 dilution of drug with 0.2 cc. of salt solution are summarized in Table I. This was a dosage of about 15 mgm./kgm. The dilution of mercurochrome before injection was 1:1,666 and, when given at once after inoculation with 0.5 cc. of culture, the dilution of drug in the peritoneal cavity was 1:3333. The culture dilutions used in these otherwise comparable tests varied from 1:1,000 to 1:30,000, that is from 10,000 to 500 times the constantly lethal dilution of 1:1 million. Of the 120 mice treated with 0.3 cc. of a 1:1000 dilution of mercurochrome, immediately after inoculation, 16.6 per cent survived; 5.5 per cent lived when treatment was postponed until 30 minutes after inoculation and 10 per cent survived when treatment was not given until 1 hour after inoculation.

An injection of 50 mgm./kgm. of drug saved 2, or 10.7 per cent, of the 28 mice inoculated with culture dilutions of 1:20,000 and 1:30,000 and treated at once. In parallel tests in which treatment was given one hour after inoculation, 4, or 16.66 per cent of the 24 mice lived. None of the 4 animals treated 2 hours after inoculation survived. Of 5 mice given 30 mgm./kgm. immediately after inoculation with a culture dilution of 1:100 million, 2 (40 per cent) lived. Neither of two mice given 20 mgm./kgm. immediately after inoculation with a culture dilution of 1:100 million lived. This inconsistency, as well as others, are explicable on the basis of the small number of mice used in some of the early experiments.

In vitro-in vivo tests. The low germicidal value of dilutions of mercurochrome used in these experiments was demonstrated in the tests in which culture dilutions and drug were mixed *in vitro* in the same proportions as those used in the *in vivo* series. Some of the mixture was injected at once and some after standing at room temperature for from 30 minutes to 2 hours.

It was evident from these experiments that a mixture of culture and of drug which had a final drug concentration of 1:500 had not lost its virulence after standing 1 hour at room temperature. The tests with mixtures of culture and final mercurochrome dilutions of 1:1000 or 1:3,333 showed no significant diminution of virulence after standing for 1 hour.

These *in vitro-in vivo* tests suggest the possibility that dilutions of

1:1,000 and 1:3,333 of mercurochrome, or dosages of 50 and 15 mgm./kgm. are more effective than a drug dilution of 1:500, with a dosage of 100 mgm./kgm. This may be correlated with the *in vivo* tests, which showed no results from treatment with 100 mgm./kgm., but definite action with dosages of from 15 to 50 mgm./kgm. Since in these *in vitro-in vivo* tests the 1:500 solution of drug did not kill the organisms, the survival of animals after inoculation with cultures exposed to weaker dilutions of drug cannot be explained on the basis of germicidal action. Moreover, had the action been germicidal, the number of mice surviving inoculation with the mixtures that had stood *in vitro* would have been greater than of those surviving inoculation with the freshly prepared mixtures of culture and drug, since controls of organisms standing in mixtures of broth and salt solution invariably died.

Summary of findings with mercurochrome alone. Although further discussion of these results is deferred until later, these findings may be briefly summarized here. It is evident that, although the *in vitro-in vivo* tests showed no germicidal action with the weak drug dilutions used, when treatment was given *in vivo*, varying culture dilutions and drug dosages being used, from none to 40 per cent of the animals survived. In the comparable tests, that is, in which treatment consisted of approximately 15 mgm./kgm. of drug, or 0.3 cc. of a 1:1,000 dilution, 16.6 per cent of the mice lived. These tests may be considered as definite proof of therapeutic action by mercurochrome, especially as in most of them the culture dilutions used were many times the lethal dose.

TESTS WITH NORMAL HORSE SERUM ALONE

In vivo tests. It was found that 0.4 cc. of normal horse serum gave marked protection against culture dilutions of 1:100,000 or higher, but that, in a smaller series treated with this amount of serum after inoculation with culture dilutions of from 1:10 through 1:10,000, no therapeutic results were obtained. The use of 0.2 cc. of serum gave complete protection against inoculation with a culture dilution of 1:100 million, none against a culture dilution of 1:5, and varying degrees of protection against intermediate culture dilutions. This protective action of normal serum was greater than had been antici-

pated, but confirmed our working hypothesis that some defense mechanism was present in such serum. Since the object of our experiments was primarily to study any influence that mercurochrome might have on this normal action of serum, rather than to determine the maximum curative effect of serum alone, most of the serum tests were done with a dosage of 0.2 cc. In this way, when the serum tests were varied by the addition of drug, an opportunity was afforded to judge any possible intensification of therapeutic action.

The failure of any mice to live after inoculation with a culture dilution of 1:5 showed that the action of normal horse serum was much less than experience has shown to be the case with immune serum, 0.2 cc. of which should protect against such an inoculation (10). Sixty-four mice (22 per cent) lived of the 290 animals that were inoculated with culture dilutions comparable to those in the mercurochrome series, that is, from 1:1,000 through 1:30,000 and treated at once with 0.2 cc. of normal, unheated serum. Thirty-six mice (24 per cent) lived of the 150 animals given similar inoculations and treated at once with 0.2 cc. of serum heated 56°C. for 30 minutes. Considering the close agreement of these percentages, it seems fair to combine the results with heated and unheated sera. Thus, 100 mice (22.7 per cent) lived of the 440 animals treated at once with serum; 37 mice (33.6 per cent) lived of the 110 mice which were inoculated with culture dilutions of from 1:1000 to 1:20,000 and treated 30 minutes later with 0.2 cc. of unheated serum. Five mice (13.8 per cent) lived of the 36 animals given similar inoculations and treated thirty minutes after with 0.2 cc. of heated serum. That is, 42 mice (28.7 per cent) lived of the 144 animals treated with heated or unheated serum 30 minutes after inoculation. The difference in these tests was in favor of the unheated serum. Six mice (10.7 per cent) lived of the 56 animals that were inoculated with culture dilutions of from 1:5,000 through 1:30,000 and were treated one hour later with 0.2 cc. of unheated serum. Only 1 of the 4 mice lived that were treated with 0.2 cc. of heated serum 1 hour after inoculation. That is, 7 mice (11.5 per cent) lived of the 60 animals treated with heated or unheated serum one hour after inoculation. The small number treated with serum makes it impossible to draw conclusions concerning the value of the two kinds of serum, when given 1 hour after

inoculation. None of the 4 mice lived that were given 0.2 cc. of unheated serum 2 hours after inoculation with a culture dilution of 1:30,000.

In vitro-in vivo tests with serum. Neither heated nor unheated serum had any marked germicidal effect on the culture dilutions employed, as the results of tests made after the serum-culture mixtures had stood at room temperature for from 30 minutes to 2 hours were either less than those obtained when injection was made at once after mixing, or they were within the limits of experimental variation.

Summary of tests with serum alone. When varying doses of serum and varying dilutions of culture were used, from none to 100 per cent of the animals were saved by serum therapy. Within the range of culture dilutions comparable to the mercurochrome series, *i.e.*, from 1:1000, through 1:30,000, 0.2 cc. of serum saved from none to 35 per cent, the average being 22.7 per cent. Little difference was found between tests with heated and unheated sera when treatment was given at once. No evidence of germicidal action was obtained with serum culture mixtures *in vitro*.

TESTS WITH MIXTURES OF MERCUROCHROME AND SERUM

In vivo tests. Owing to the protective action of serum alone against culture dilutions of 1:1 million or higher, the valid tests with mixtures of drug and serum are those in which the culture dilutions used were from 1:5 through 1:20,000. Except for the test with a 1:5 culture dilution, some of the animals in every experiment were saved by the combined treatment, as compared with some complete failures in both of the other series. Of the 404 animals inoculated with culture dilutions of from 1:1,000 through 1:30,000 and treated at once with a mixture of 0.3 cc. of 1:1,000 mercurochrome and 0.2 cc. of heated or unheated serum, 173, or 42.8 per cent, lived. Of these, 254 received a mixture of mercurochrome and unheated serum, 112 mice (44 per cent) living, and 150 received a mixture of mercurochrome and heated serum, 61 mice (40.6 per cent) living. As in the series treated with serum only, this difference between heated and unheated serum is insignificant.

Treated with drug-serum mixtures, in the same proportions, but 30 minutes after inoculation with culture dilutions of from 1:1,000

through 1:20,000, 62 mice, or 44.2 per cent of the total of 146 animals, survived. Of these animals, 110 received drug and unheated serum. Of these, 53 (48.1 per cent) survived. Of the 36 mice treated with

TABLE I

Summary of comparable in vivo tests with (a) 0.3 cc. of 1:1,000 mercurochrome and 0.2 cc. of salt solution; (b) 0.2 cc. of serum and 0.3 cc. of salt solution; and (c) 0.3 cc. of 1:1,000 mercurochrome and 0.2 cc. of serum

Mice treated after inoculation with 0.5 cc. of culture dilutions from 1:1,000 through 1:30,000.

TREATMENT	TIME OF TREATMENT AFTER INOCULATION											
	At once			30 minutes later			1 hour later			2 hours later		
	Total number of mice	Lived		Total number of mice	Lived		Total number of mice	Lived		Total number of mice	Lived	
		Number	Per cent		Number	Per cent		Number	Per cent		Number	Per cent
Mercurochrome, 0.3 cc.; salt solution, 0.2 cc.	120	20	16.6	36	2	5.5	20	2	10			
Serum, unheated, 0.2 cc.; salt solution, 0.3 cc.	290	64	22.0	110	37	33.6	56	6	10.7	4	0	0
Serum, heated, 0.2 cc.; salt solution, 0.3 cc.	150	36	24.0	36	5	13.8	4	1	25.0	4	0	0
Total tests with serum 0.2 cc.; salt solution, 0.3 cc.	440	100	22.7	144	42	28.7	60	7	11.5	8	0	0
Mercurochrome, 0.3 cc.; serum, unheated, 0.2 cc.	254	112	44.0	110	53	48.1	36	4	11.1			
Mercurochrome, 0.3 cc.; serum, heated, 0.2 cc.	150	61	40.6	36	9	25.0	8	1	12.5			
Total tests with mercurochrome, 0.3 cc.; serum, 0.2 cc.	404	173	42.8	146	62	44.2	44	5	11.3			
Untreated animals inoculated with 0.5 cc. of a 1:10 million dilution of culture	46	0	0									

drug and heated serum, 9 (25 per cent) lived, a difference in favor of the unheated serum. Treated one hour after inoculation 5 (11.3 per cent) of the total of 44 mice lived. Of this series, 36 were given

drug with unheated serum. Of these, 4 (11.1 per cent) lived. Of the 8 treated with drug and heated serum, 1 lived.

In vitro-in vivo tests with mixtures of drug and serum. No reduction of virulence was obtained when mixtures of culture, drug and serum were allowed to stand at room temperature for from 30 minutes to 2 hours.

Summary of tests with mixtures of mercurochrome and serum. Such mixtures, although not germicidal, saved varying numbers, up to 100 per cent in some series of the animals that were treated at once after inoculation. 173 mice (42.8 per cent) lived of the 404 mice inoculated with culture dilutions of from 1:1000 through 1:20,000 and treated at once with a mixture of 0.3 cc. of 1:1000 mercurochrome and 0.2 cc. of heated or unheated serum.

DISCUSSION

If the results obtained in comparable series are analyzed statistically, the validity of the comparisons which may be made between the results with the three different methods of treatment may be determined. These comparable tests have been summarized in Table I.

Yule (11) says: "The value of P is the probability that a set of observations will occur giving a group of deviations from theory, *i.e.*, a value of x^2 which is more improbable than that observed." That is, when the value of P is low, the probability of obtaining different results with further experiments is low and the results are, therefore, significant. Miss Leah Seidman of this Institute has been kind enough to determine the values of x^2 and P for us for the figures given in the tests in Table I, which were done at once and thirty minutes after inoculation.

TIME OF TREATMENT AFTER INOCULATION	MERCUROCHROME ALONE VERSUS SERUM ALONE		MERCUROCHROME ALONE VERSUS MERCUROCHROME AND SERUM MIXTURE		SERUM ALONE VERSUS MERCUROCHROME AND SERUM COMBINATION	
	x^2	P	x^2	P	x^2	P
At once	2.0569	0.157	27.202	0.000	38.8421	0.000
30 minutes	9.2730	0.00229	17.257	0.0000	7.0179	0.00815

It is evident from the values of P determined that, while the difference between the results with mercurochrome alone and with serum

alone are not significant, the differences between drug alone and the combined treatment, or between serum alone and the combined treatment are significant in the tests done at once after inoculation, as the value of P in these comparisons is zero. One therefore feels justified in concluding that the combined treatment is more effectual than the action of either drug or serum alone.

The results secured in mice which were infected intraperitoneally with multiple lethal doses of pneumococci (Type I) when treated with the mercurochrome-serum combinations suggests the desirability of further studies to determine why the mixture is so superior to its individual components. It would seem that the explanation can scarcely depend upon a direct germicidal action of the mixture, since *in vitro tests* with the mixture showed no germicidal action in one hour at room temperature. It would seem probable that the favorable results are dependent upon a stimulation of the normal protective functions of the animal, or upon the formation of some unknown compound *in vivo*. The favorable results secured with the combination of normal horse serum and drug suggest the desirability of further tests of the efficacy of the latter in combination with immune sera. One preliminary test suggests that the efficacy of such serum will be heightened.

SUMMARY

Series of mice, inoculated with various dilutions of pneumococcus cultures, have been treated with mercurochrome alone, with horse serum alone and with mixtures of mercurochrome and serum. The following results have been obtained.

1. Mercurochrome alone had definite therapeutic action, when used in dosages of from 15 through 50 mgm./kgm., better results being obtained with moderate doses than with 100 mgm./kgm. In the many series of animals studied, from none to 40 per cent, treated with mercurochrome, survived, although the inoculations were generally many times the lethal dose. In tests in which treatment consisted of 0.3 cc. of a 1:1000 mercurochrome solution plus 0.2 cc. of salt solution, 16.6 per cent of the 120 mice lived that were so treated at once after inoculation, 10 per cent surviving when treatment was delayed one hour after inoculation.

2. Normal horse serum had marked protective action against culture dilutions of 1:1,000,000 or higher. Of the 440 mice treated with 0.2 cc. of serum plus 0.3 cc. of salt solution at once after inoculation, 22.7 per cent lived.

3. Mice treated with mixtures of mercurochrome and serum showed a markedly favorable therapeutic response as compared with mice receiving either drug or serum alone. Of the 404 mice treated with a mixture of 0.3 cc. of a 1:1000 dilution of mercurochrome and 0.2 cc. of serum, 173 animals, or 42.8 per cent, lived, as compared with 16.6 per cent saved by the drug alone or 22.7 per cent saved by serum alone. While a statistical analysis shows that the differences between the results with drug alone and serum alone are not significant, valid comparisons may be made between the results with drug alone and the combined treatment and between serum alone and the combined treatment.

4. The therapeutic action shown by mercurochrome and by normal horse serum separately and by the mixture is unrelated to direct germicidal action, as evidenced by the failure of *in vitro* mixtures of culture dilutions with these substances to show any diminution in virulence.

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Since it is obviously impossible to publish the protocols of all of these experiments, the authors will be glad to furnish them to anyone interested in further details of this study.

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PROBLEMS OF HUMAN GENETICS[1]

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Mr. President, Ladies and Gentlemen: I want to express my deep appreciation of the honor which you have conferred upon me by inviting me to deliver a Herter Lecture. We, in Europe, are well aware that such an opportunity is held to be one of the greatest privileges that can be offered to a medical research worker and teacher in your own country.

Broadly speaking, the members of the medical profession have hitherto failed to acquaint themselves with the problems belonging to human genetics and the results thus far obtained. The causes for this indifference are various. First of all, the difficulties connected with the study of genetics, which also entails the understanding of not too simple a terminology, are frequently overestimated. But these obstacles are certainly not greater than in other branches of medical science. Secondly, physicians seem to think that genetics have no direct connection with practical medicine, or with diagnosis and treatment. But in reality genetics have a bearing upon the physician's activities no less than that of chemistry, bacteriology and other sciences, all of which are indispensable for a physician because they all help him to understand the mechanism and the genesis of pathological conditions. We cannot hope to find out a genuinely appropriate treatment for a sickness until we have available a most thorough knowledge of its genesis, and we are certainly wrong to look for the causes of pathological conditions outside the organism only and to take into account only exogenous influences. Endogenous potencies alone bring about the development of an organism that starts from a fertilized ovulum; they govern its evolution, its functional activity and involution. Disturbances of these endogenous potencies are not

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always due to influences from outside; frequently they are nothing but the consequence of innate variations, of deviations or deficiencies of these very potencies.

Many physicians argue somewhat in the following way: "If we assume that a given disease is not produced by bacterial, toxic or other exogenous injuries but is purely for the most part the consequence of abnormal primordia, in other words, if we say that it is constitutional, how shall we be able to fight against it successfully, seeing that we cannot change the primordia"? These men disregard the fact that the therapeutic results will be just the same, regardless of our attitude towards genetics. But surely, only the right attitude can save superfluous efforts in combating the disease. And surely, even if we cannot change the primordia, we may be able, at least sometimes, to modify their phenotypical manifestations, to compensate their effect by various procedures.

It seems to me that the most important cause of the antipathy of physicians to genetics is the fact that the results of this branch of medical research work are not to be obtained by the usual morphological, chemical, serological or similar technical methods, *they are not visible to the eye*—not even with the aid of a microscope, ultramicroscope or in a test-tube—but they are available for all those who know how to draw logical conclusions from facts presented by nature, and from clinical and pathological observations made in everyday practice. Many physicians are still afraid that they may be looked upon as philosophers instead of natural scientists, if they use, as the only scientific method, *thinking*, and if they do not base their conclusions safely upon clinical and laboratory data.

The problems of human genetics are not exhausted, as many assume, by stating what morphological or functional characteristics of the organism may be inherited and what type of inheritance they may show, whether dominant, recessive, sex-linked, and so on. The chief problem lies in the recognition and the most complete isolation of what we may call Mendelian units or primordia. It is necessary to reduce the phenotype, that is, the finished organism, to its genotypical basis; we must determine what part of it was represented by the germ plasm and what part of it was present as a latent potential energy in the fertilized ovulum. We know well from the results obtained

from general genetics that many quite different phenotypical characteristics may be due to one and the same potential energy of the germ plasm, that is, to one unit, while, on the other hand, one phenotypical trait may be produced by quite a number of different primordia. The riddle of the fertilized ovulum is not to be explained by a sort of homunculus, or a miniature edition of a human being; it does not cover merely a sum of morphological and functional characteristics in a latent form, but represents an accumulation of potential energies of quite a different kind; it contains categories of quite a special type, different from those of morphology or physiology. Primordia for a definite stature, for hair pigment, for the shape of the nose or the external ear, on the one hand; primordia for metabolic functions, psychic features and other functional characteristics; primordia for the quickness of evolution and for the wear and tear of different organs, for the reactivity towards exogenous influences and many other constitutional traits,—all these may be represented by the germ plasm without giving even a semblance of the finished human being at all.

The relation of the phenotype to the sum of the primordia in the germ plasm, that is, to the genotype, is about the same as the relation of a well organized, big factory to the sum of minutely detailed plans, architectonic, technic, mercantile and financial—making up the whole organization of the future factory as a sort of potential representation. In one more point of prime importance this analogy may be maintained. Just as one special detail of the whole plan—it may be an architectonic, mercantile or of any other kind—is entirely without significance by itself, if separated from the whole plan, so a primordium or a complex of primordia separated from the total sum of the genotype becomes senseless and means nothing. Only as a part of the genotype and in close operation with all other primordia does it represent the most powerful and most marvellous potential energy.

The methods applicable to human genetics are quite different from those of general genetics based upon breeding experiments with plants and animals. We have to collect carefully the spontaneous breeding experiments with human beings performed by nature, and have to use these instead of experimental breedings. As a matter of course, statistical methods only are to be applied in the evaluation of these spontaneous matings. We shall be able to identify special normal

primordia only if we observe and analyze carefully the consequences and manifestations of their pathological alterations. From pathology we have to draw our inferences for the normal genotype. That seems to be the only way to the ideal aim of analysing the genotype

FIG. 1. EUNUCHOID WITH CONSTITUTIONAL (HEREDITARY) GIGANTISM

of human beings similarly to the analysis of the genotype of plants or lower animals, and particularly of the banana-fly (Drosophila) performed by general biologists and geneticians under the leadership of T. Morgan.

Despite the great difficulties in studying human genetics from these standpoints and despite the fact that we are only in the beginning of

these studies, we are able, even today, to isolate quite a number of primordia in the sense of Mendelian units. I shall not enumerate the complete collection of primordia whose presence in the germ plasm has to be taken for granted, as the pigmentation of skin, hair and iris, the shape and type of hair, nose, ears, hands and so on, but I want to discuss tonight just a few selected primordia which illustrate some particular points of clinical interest.

The height of the body, for instance, is undoubtedly determined by a primordium in the germ plasm; hence it is a constitutional characteristic. This has been established by observation of different families and different races. What has become a racial must have been previously a familial characteristic; that is, a constitutional characteristic. Physicians are inclined to attribute abnormalities in growth to endocrine disturbances, and it is a matter of fact that alterations of thyroid, pituitary or gonadal function may be associated with disorders of growth. But the tendency to refer to the endocrines every variation in growth goes so far as to connect even racial differences in height with glandular differences (Keith, Stockard). But we must not forget that endocrine hormones are only one factor among those that influence the height of the body, and that in lower organisms that do not possess any endocrine glands at all, such as insects, protozoa or plants, variations in size are obviously dependent on special primordia which influence the growth directly and act upon the cellular activity without any intermediate hormonal influence. Four years ago I had the privilege, here in Baltimore, of pointing out in detail that the endocrine glands of vertebrates are interposed only between certain chromosomal potencies representing the primordia, on one hand, and, on the other, the peripheral organs where these primordia become actually manifest, where they act. The endocrine glands represent a sort of multipliers or condensors of certain primordia upon which they themselves are dependent. I need not again discuss this interesting problem tonight, but shall limit myself to illustrating it with the help of certain examples.

Figure 1 shows a man with a typical eunuchoid gigantism. He is about 30 years of age, has a height of 202 cm., with markedly long extremities and has infantile genital organs. He never has had any sexual desire, has no beard and very little hair in the axillae and pubes. Gigantism associated with hypogenitalism used to be considered as

purely the result of insufficient endocrine function of the gonads. But, as I pointed out years ago, only a limited number of all eunuchoids grow in this way; the majority of them do not develop any gigantism at all. Therefore, we have to look for some other explanation. We get it in our case when we learn that the father of the patient is about the same size as his son, that a brother is 196 cm. in height and that two sisters are also unusually tall. In this family the inherited constitutional primordium for overgrowth is obvious. That this primordium does depend upon something quite different from the endocrine function of the gonads is also clear, inasmuch as no other member of the family shows symptoms of hypogenitalism. Hence, we draw the inference that the gigantism is not the pure consequence of the hypogonadism and we may even ask whether this latter may not be a consequence of the abnormal primordium for overgrowth, since this primordium influences, without any doubt, the proliferation of osseous tissue at the epiphyseal cartilages not only directly but also through some endocrine hormones. The activity of a normal as well as of an abnormal primordium for growth bears relation to certain endocrine organs also; they are dependent upon this primordium to a certain extent and may show abnormalities in their structure or function if the primordium for growth is not normal. The chief point, however, is that what is inherited in such a family is not a special endocrine disturbance, but a special abnormality in height. What I have emphasized is not based solely upon one or quite a few exceptional observations; the case that I mentioned was used as an instance only and represents a typical occurrence. Therefore, we meet sometimes with families whose different members show different types of overgrowth or undergrowth, dependent on the various participation of different glands in producing the abnormal growth. I should like to refer only to some examples discussed here four years ago.

What is true for abnormalities of growth holds true also for abnormalities of evolution and involution. Precocious as well as delayed puberty, longevity as well as premature senescence of the organism, may be due to abnormal primordia working partially through certain endocrine organs.

The fat amount all over the body and the type of its distribution over its surface are certainly dependent on special primordia that

influence the fat tissue itself as well as some endocrine organs and vegetative nervous centers so far as they are connected with the regulation of fat metabolism in general. Figure 2 shows a lady, 55 years of age, affected with a marked obesity which had been present for about

FIG. 2. INTRASELLAR TUMOR IN A 55-YEAR-OLD LADY WITH CONSTITUTIONAL (HEREDITARY) OBESITY

FIG. 3. THE SON OF FIG. 2; 34 YEARS OF AGE; 125 KG. WEIGHT

30 years. The lower part of the body is more especially implicated and the lipomatosis of the legs is quite considerable. Endocrine disorders were not to be found; more particularly there was no evi-

dence of an insufficient thyroidal or gonadal function. She had menstruated regularly from her 12th to her 53rd year and had had four children. Only after routine examination did we find a markedly enlarged sella turcica suggestive of an intrasellar tumor. Other symptoms or complaints due to this tumor were entirely absent. Everyone is inclined to-day to assume a pituitary origin for an obesity if he meets with such a coincidence of obesity with an enlarged sella; but one may forget that proof for such a causal connection is wanting. In our case at least we could make the statement that the obesity was a constitutional, inherited one, without any doubt, and that even the particular lipomatosis of the legs was a familial characteristic. Both parents had been extremely obese and three of the four children showed the same condition. The son, 34 years of age, has a body-weight of 125 kgm. (Fig. 3). An X-ray taken in two of these stout children did not reveal any pathological changes of the skull, nor were any other symptoms of an endocrine disturbance to be detected. Therefore, we can hardly assume that all these members of the obese family had inherited an alteration of the pituitary gland, and we may ask a question analogous to that in our discussion of the case of eunuchoid gigantism. Is it a pure accident that a woman with a constitutional primordium to obesity developed a pituitary or, let us say, an intrasellar tumor; or may not this tumor be the indirect consequence of the pathological primordium, since this primordium may influence the functional activity of the pituitary gland also? It is paradoxical, but it seems to me rather probable that a pathological growth of the pituitary need not always be the cause of a present obesity, but may even be the consequence of the efficacy of a constitutional primordium for obesity.

The hereditary character of certain types of obesity is proved also in animals. In Dr. Danforth's laboratory at Stanford University I saw a strain of quite fat mice which transmitted this special character to their offspring as a dominant Mendelian unit. Danforth found that this factor for obesity was a lethal one, if it occurred in homozygous form. This observation is of interest particularly because we know from the fine work of Ph. E. Smith that a lesion of the tuber cinereum without an involvement of the pituitary gland may be followed by an extreme building up of fat. Some endocrine glands as well as some centers

in the brain may give rise to obesity, but they all are themselves dependent on the securing by the primordium of an appropriate amount of fat building. They all may be involved if this primordium is changed,—if we have to deal with a constitutional obesity.

These different examples demonstrate as clearly as possible that endocrine disorders cannot be understood completely without a certain knowledge of constitutional pathology, that is, of human genetics. Endocrinology without this complement is, in my opinion, not able to elucidate many pathological conditions which are considered today (but without much real foundation) to be wholly of endocrine origin. It struck me as rather peculiar that, in his review of my book on *Endocrine Secretion*, an American author should write the following sentence in the *Archives of Internal Medicine:* "At present one may question whether the introduction of such concepts as genotype, personality and heredity, without further analysis of the mechanisms of these processes, does not contribute more fog than clarity to an already difficult field." This sentence proves how important, but at the same time, how difficult it is to promulgate the science of genetics among physicians. It is always hard to make popular among the medical profession something whose far-reaching significance is not obvious at first sight.

A very instructive example for the study of human genetics is the peripheral motor apparatus, including bones, joints and muscles. My assistant, Dr. Berta Aschner, has been doing an extensive research along these lines during the past few years. Of the vast material available, I can pick out only a few special points of interest.

Polydactylism, for instance, is usually considered as a simple dominant Mendelian character. But a thorough investigation of many families described in the literature reveals that not only polydactylism but also its special type is inherited. In one family it is an accidental thumb, in another an accidental fifth or third finger which is found through many generations in several members. Therefore, a special localization factor linked with the factor for polydactylism is to be assumed. Such an assumption has many analogies in general genetics. If we have to deal with a Mendelian unit producing polydactylism in some families, then we normal individuals possess a unit securing the formation of only five fingers and toes. That is a simple

and forceful inference deduced from pathology for the normal. This unit which secures the normal number of fingers must be, it would seem, closely related to some other units responsible for the normal number of osseous radii in the extremities, for the normal number of extremities as a whole and for the adequate number of different organs in general. The most extreme degree of supernumerary development of organs would be a complete reduplication of the organism developing from one fertilized ovulum, that is, the formation of identical twins. It is a well established fact that the tendency to twin-births, and particularly to the formation of identical twins, is an inheritable characteristic (Davenport, Bonnevie, Dahlberg). In animals the inheritance of reduplication or, rather, the multiplication of extremities or other organs is sometimes quite evident; in human beings these cases are too rare, their propagation so exceptional that we cannot expect to prove their inheritance.

In the banana-fly, for instance, a strain with a supernumerary extremity has been obtained by Hoge, one of Morgan's students. Danforth, at Stanford University, is studying, at the present time, the type of inheritance of an accidental fifth extremity in a strain of white mice. It is interesting that this accidental extremity has six toes and that this observation—polydactylism in a supernumerary extremity—has been commonly made by other authors. A strain of goat with a supernumerary horn has been described by Gredler, and even a reduplication of the head was found in 3 individuals of one litter of a snake (coluber constrictor) by Mitchell. Dasypus novemcinctus has a racial tendency to multiplication. One fertilized ovulum gives rise to four young individuals as a rule, and an inheritable reduplication of some armour-plates is not infrequent in this species. Newman speaks of a "doubling tendency" in dasypus. It was Bateson who emphasized in general the existence of a "complete series of stages intermediate between total and partial duplicity." Dr. Aschner was able to collect several observations reported by different authors bearing upon an alternation of different kinds of multiplication in the same human family: polydactylism, reduplication of a whole extremity, reduplication of the whole upper part of the body (thorakopagus) and twinning. It seems therefore probable that there exists a more or less uniform complex of primordia that make possible the

development of the normal number of each organ and of each part of the organism in general. Polydactylism would represent only a special and rather frequent type of an abnormality of this complex of primordia.

The existence of a localization factor, which is to be assumed in polydactylism, is not to be denied in syndactylism; the special localization of the insufficient or total separation of fingers is just as well an inherited characteristic as the special localization of a supernumerary finger.

The discussion of the problem of polydactylism offers the opportunity of touching upon the problem of the linking of genes in human beings. We owe to Bardet, Biedl and other authors the knowledge of a typical hereditary pathological condition. This syndrome is characterized by the combination of polydactylism and syndactylism with obesity, genital hypoplasia, retinitis pigmentosa, intellectual deficiency and malformations of the skull. The complete syndrome is not always developed. Each of these symptoms may occur also as an isolated phenomenon in certain members of the family, just as it is to be found singly as a hereditary trait in other families. There is no doubt that only the science of human genetics can aid us in understanding the mechanism of such a pathological condition and that the assumption of a linkage of several pathological primordia, i.. the sense of modern genetics, is here to be taken into account.

A linkage of two pathological primordia is also to be considered if we learn that, among seven families with a hereditary deficiency of the patella reported by several authors, Dr. Aschner found three of them showing at the same time a hereditary aplasia of the nails of the thumbs. As the affected members of these families had with one single exception both deformities, an aplasia of the patella together with the aplasia of the thumb-nails, the supposition of a linkage of these two primordia is highly probable and we draw again the conclusion from pathology to normal: the normal development of the patella and of the thumb-nails seems to be dependent on the presence of at least two primordia localized in the same chromosome.

There is no doubt about the inheritance of a congenital dislocation of the hip-joint. What is it in the fertilized ovulum that induces this pathological condition, or in other words, what if it be represented by a

primordium? This question has been studied by Dr. Aschner in the following way: She collected 157 cases of congenital dislocation of the hip in which some other congenital orthopaedic deformations happened to be associated with it. A selection of special cases was carefully avoided. With all statistical precautions the fact could be established that each of the different congenital orthopaedic abnormalities accompanied the congenital dislocation of the hip just as frequently as it is to be met with among congenital orthopaedic deformations in general. Only the congenital dislocation of other joints has been found associated with the congenital dislocation of the hip much more frequently than it occurs without it among all other congenital orthopaedic abnormalities. There are even exceptional cases with congenital dislocations of several or nearly all joints. From these statements the conclusion is warranted that there exists a primordium or a complex of primordia in the normal genotype which effects the normal and correct position of the constituents of the joints in general, and that the congenital dislocation of the hip is due not only to an anomaly of such a primordium alone but also to a determining localization factor.

Quite an analogous statement was made by Dr. Aschner for cases of congenital joint-contractions. The combination of club-hands with other sorts of congenital joint-contractions (club-feet, contractions of fingers, elbows, shoulders, hips, knees) is to be found more frequently than the combination with congenital dislocations of joints, with polydactylism, deficiencies of bones or other congenital orthopaedic conditions. Hence some primordia must be responsible for a normal mobility and activity of joints in general. A special localization factor seems to be of importance here again.

To illustrate the significance of such a localization factor I wish just to mention a family observed by Vogl in Vienna. Four brothers and their sisters were all affected by a chronic ankylopoetic spondylarthritis; and finally I would cite a very peculiar observation of Durban concerning the rupture of the tendon of the right extensor digiti III, caused by a quite inadequate, inconsiderable traumatism in a mother and in her son. There is scarcely any doubt that in these families the affected part of the body, that is the vertebra in the first, the tendon of the extensor digiti tertii in the second family represented a *locus*

minoris resistentiae resulting from some sort of poor constitutional development and structure of this very organ or tissue. It matters not whether such a constitutional biological inferiority of an organ may or may not be discoverable, before the onset of the disease, by morphological, chemical or other sorts of examinations. The fact of the existence of such an inferiority disposing to pathological conditions is not to be denied in the presence of observations such as have just been cited. This statement is based not upon results gained by our usual methods of investigation but upon a logical and necessary conclusion from facts presented by nature itself. *Biological inferiority of an organ* or a tissue is therefore a term taken from genetics and based upon genetical facts, independent of a possible confirmation by morphology or chemistry.

Several years ago I was studying with my associates, Dr. Spiegel and Dr. Aschner, the families of patients affected with a peptic ulcer of the stomach or duodenum. First, we could confirm on a large scale the fact, well known to every experienced physician, that there are families in which a peptic ulcer occurs in several members of several generations. Even the special clinical picture may be identical in several members of the family. The statistical investigation of 255 cases of certified peptic ulcer showed that if both parents of an ulcer patient had not suffered from the stomach, 10.8 per cent of their children developed ulcer; if one of the parents had chronic stomach trouble, then 25.7 per cent of their children suffered from ulcer. Secondly, we found that cancer of the stomach was considerably more frequent among the parents of ulcer patients than among the parents of 400 control patients affected with various diseases other than stomach trouble. Hence we may draw the conclusion that in these families something is transmitted by the germ-plasm which is responsible for the development of peptic ulcer as well as for cancer of the stomach, and without any doubt bearing upon the quality, structure and reactivity of the stomach itself, inasmuch as by no means all of the cancer cases in these families were to be considered as due to malignant degeneration of a peptic ulcer. We spoke of a biological inferiority of the stomach disposing to an ulcer as well as to a cancer. It is a secondary question only whether we may be able to detect an anatomical or chemical basis for such a constitutional inferiority or not; the

fact of such an inferiority is well established simply by genetical investigation. Our statement of a genetical interrelationship between peptic ulcer and cancer of the stomach has been confirmed by Grote and by H. Strauss in Germany. I believe that a careful study of this interesting question afforded by the enormous material available in some of your great medical centers, particularly at the Mayo Clinic, will reveal nothing additional to what we could find in our European material.

Concerning the heredity of cancer, speaking generally, it may be said that its existence needs no further discussion if we recall the remarkable breeding experiments of Maud Slye with mice strains affected by cancer. A thorough study of a population of 6000 mice revealed the genotypical disposition to malignant growths, being a recessive Mendelian characteristic in mice. What is true for mice holds true in principle also for men and the pedigrees of human families carefully studied, as those described by A. S. Warthin, H. G. Wells and other authors, prove the importance of inheritance in the etiology of cancer. Some years ago I pointed out that all known facts concerning the genesis of human cancer are in favor of the supposition that two Mendelian factors at least are cooperative in the production of a constitutional disposition to this disease. One factor apparently determines the general disposition to neoplastic proliferation of tissues in general; the other is a localization factor again determining the special organ affected by the growth. There is no doubt about the existence of such a constitutional biological inferiority of certain organs in some families who develop a cancer in this very organ through several generations. It is impossible to discuss in this address all the arguments available to prove the correctness of our hypothesis. I wish to emphasize only the accord of this supposition with our results obtained in studying the families of peptic ulcer patients.

The problem of constitutional biological inferiority of an organ disposing to pathological conditions is illustrated also by the investigations performed by C. Stein and myself in families of patients affected with otosclerosis and hereditary degenerative atrophy of the acustic nerve. There is an intimate genetic relationship between both kinds of impairment of hearing including also the congenital constitutional deaf-and-dumbness. We were unable to agree with the usual assump-

tion that different kinds of pathological Mendelian primordia produce these different types of ear diseases. We emphasized as highly probable that a genotypical alteration of the auditory organ, that is, its constitutional biological inferiority due to an abnormality of the primordia which should bring about the normal development, structure and function of the auditory organ, is the common basis for the evolution of all these kinds of diseases, the otosclerosis as well as the progressive degeneration of the acustic nerve and the deaf-mutism.

An interesting illustration of the problem of the relation between genotype and phenotype, and of the question what a constitutional disposition to a disease means, is yielded by the study of the so-called hemolytic anemia or hemolytic jaundice. The separation of two types of this disease, one congenital-constitutional and one acquired, is not quite satisfactory on account of the statement that some of the relatives of a patient affected with an apparently acquired hemolytic anemia or jaundice may show quite well defined symptoms of the same condition without being sick at all. Enlargement of the spleen, increased fragility of red blood corpuscles, urobilinuria or increased fragility of red blood corpuscles, urobilinuria or increased bilirubinemia may indicate an abnormal destruction of erythrocytes in some healthy but obviously disposed members of those families. They are healthy so long as the bone marrow and the liver are able to compensate for the increased destruction of erythrocytes; they fall ill with a hemolytic anemia or hemolytic jaundice as soon as the overactivity of the bone-marrow and of the liver fails to compensate, on account of an exhaustion of these overstrained organs. Some accidental events, such as pregnancy, syphilitic infection or other infectious or toxic influences, may bring about such an exhaustion. What is determined and transmitted by the germ plasm in those families is an apparently short duration of life of the red blood corpuscles varying under normal conditions between three and four weeks. An inheritable diminution of this time brings about the constitutional disposition to develop a hemolytic anemia or jaundice. This will become obvious as soon as a sufficient compensation for the constitutional abnormality is no longer possible and may happen also at a very early age. These cases are called congenital but fundamentally they are not different from the acquired ones.

In the cases of hemolytic anemia or jaundice the constitutional disposition to the disease may be detected prior to its onset. To find out a constitutional disposition to other diseases, too, and to discover it in an individual before he has developed the ailment was always greatly desired by physicians from the oldest time until today. When we employ the terms *habitus phthisicus, habitus apoplecticus, emphysematosus or arthriticus*, we acknowledge the fact that a particular general make-up may be associated with a constitutional predisposition for certain diseases. When we learned from Kretschmer that a special type of habitus is frequently related to special psychic features of an individual, we obtained knowledge of a very interesting quality of the human genotype. Genes or primordia whose activity produces the characteristic features of the general make-up of the individual are responsible at the same time for the development of a special mental attitude and temperament. It does not interest us now whether they may act directly upon both the somatic and psychic characters of a man, or whether there exists a close relationship (linking) between two different groups of genes. What is of importance for the clinician is the statement that we may recognize some quite different and apparently quite intimate functional characteristics of an individual if we pay attention to certain external morphological features of his body. George Draper is the most outstanding man who is trying to bring some light on this problem which may be directly available for clinical medicine. He feels that there exists quite a characteristic and specific relationship between particular morphological traits of the body and the constitutional disposition to certain diseases much more far-reaching and much closer than we are in the habit of assuming today. His material, carefully gathered and studied will certainly be of vast importance as soon as it becomes large enough for a statistical evaluation. Draper's optimistic attitude on this subject may be justified by our experiences with lower organisms.

Nilsson-Ehle, a Swedish botanist and genetician, found, some years ago, that barley possesses either a specific disposition or a specific immunity against the infection with a little worm (*Heterodera schachti*) which injures the roots of the infected plants. Furthermore, he established the fact that the behavior towards the parasite was a constitu-

tional inheritable character of the strain of barley. Immunity was transmitted in the breeding experiment as a dominant, disposition as a recessive character. But what is of particular interest for us, the immune and the susceptible barley looked absolutely alike; the reactivity towards the parasite was the only trait different in both sorts of barley. A genotypical, constitutional difference was present but could not be detected by a morphological examination of the strain.

Morgan and Raymond Pearl, on the other hand, found a close relationship between special morphological characters of the banana fly (Drosophila) and the duration of life or the reactivity of these insects towards different influences. Analogous experiences made by breeding experiments with different animals confirm the fact that certain primordia or genes responsible for some special morphological features may govern directly or indirectly at the same time more intimate reactions of the organism and may betray them even before their actual manifestation.

Let us hope that Draper will find human beings behaving more like Drosophila than like barley, if we are permitted to analogize his studies in men with the findings of general biologists in lower organisms!

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BOOK REVIEWS

General Bacteriology. By EDWIN O. JORDAN. 9th edition, 778 pp. (*W. B. Saunders Co., Philadelphia, 1928.*)

The latest edition of this excellent textbook has been brought up to date in most chapters, particularly those dealing with matters of much current interest. There is new material on the streptococcic diseases, tularemia, infectious abortion, disinfection, filterable virus and protozoan diseases, certified milk with its problems and other subjects. The discussion of immunity and infection has been improved from a pedagogic standpoint. There are other new features of value.

The bibliography includes many quite recent articles and is of value to the more inquisitive type of student and to the investigator.

The arrangement of material is convenient and its presentation is, as it has been in past editions, very readable. It is clear without being wordy, conservative without being dogmatic and accurate without being pedantic. The tabulation of generic characters at the heading of each chapter is helpful to students and might be extended advantageously.

In this, as in every textbook, there are certain omissions. Those in this case may be said to be, in general, of lesser importance to the medical and elementary student. For example, there might be included some discussion of allergy in relation particularly to scarlet fever, rheumatism and tuberculosis. Dissociation of bacterial types is assuming more and more importance and a summary of the fundamental ideas concerning this phenomenon might be added to the paragraphs on variation and mutation. The chapters on anaerobes might be improved from a teaching viewpoint by a tabulation of the "metabolic gradient" that exists among these organisms.

M. F., JR.

Asthma, The Diagnosis and Treatment. By WILLIAM S. THOMAS, M.D. 279 pp. $7.50. (*Paul B. Hoeber, Inc., New York, 1928.*)

This book contains a clinical discussion of a group of symptoms, together with methods of diagnosis and treatment.

In the section devoted to vaccine therapy one can find numerous statements that are certainly open to question. A very small chapter is given to the discussion of pollen asthma. There is an extensive bibliography. The book contains much that is of general interest, but cannot in any way be regarded as a reference work.

Paul B. Hoeber, Incorporated, have published this treatise of 279 pages at a price of $7.50. It is printed on very expensive paper. Of the 279 pages, 60 have

been inserted which have no printed matter upon them except, perhaps, the number of the chapter. Such a method undoubtedly increases the cost of publication and makes the purchaser carry an unnecessary burden. The binding of the book, with the unnecessary blank pages, does not in any way increase the value of the publication to the progressive physician or student who buys books to read and not for show; nor does it make it worth the price that is asked by the publishers.

L. N. G.

The Endocrines in General Medicine. By W. Langdon Brown, M.A., M.D., F.R.C.P., Physician to St. Bartholomew's Hospital. Belonging to the Series of Modern Medical Monographs, Edited by Hugh Maclean, M.D., D.Sc., F.R.C.P., Professor of Medicine, University of London. 143 pp. $3.00. (*Paul B. Hoeber, Inc., New York, 1897.*)

Physicians and medical students owe the author a debt of gratitude for publishing this little volume. It gives, in a concise form, the essentials of our present knowledge concerning the various symptom-complexes believed to be due to disturbed functions of the endocrine glands, while giving useful suggestions as to substitution therapy, so far as our limited knowledge along this line permits.

It is apparent that the author has been a careful and discriminating student of the diseases of the ductless glands and exercises proper restraint with regard to the possibilities of combating the various syndromes from a therapeutic standpoint. In a brief work of this kind there is no bibliography, but one is struck with the rarity with which the author refers in the text to the excellent work done by Continental and American investigators, his citations being restricted largely to researches of British students on the subject under discussion.

Following two very interesting chapters on "The Biology of the Endocrine System" and "The Endocrine System in Childhood," the symptomatology of the diseases of the individual endocrine glands is dealt with in a very convincing and interesting way. There are concluding chapters on "Endocrines and the Psychoneuroses," "Endocrine Therapy," and "The Future of Endocrinology," which will be of great interest to endocrinologists.

The volume will prove of great value to those who desire a concise and sane review of our present knowledge of this interesting field of Internal Medicine.

T. B. F.

Fighters of Fate. By J. Arthur Myers. With an introduction by Charles H. Mayo. 318 pp. $3.00. (*The Williams & Wilkins Company, Baltimore, 1927.*)

A little book in praise of man's courage. Most of us, through the greater part of our lives, are able to repress from our consciousness the ultimate tragedy. To some individuals, the knowledge of their end is prematurely vivid. How such people adjust bravely to the problem of living cheerfully, how they "burn their

own smoke"—in Osler's phrase—is made clear by these life-stories. Many of the names are famialiar to most of us. To a public that no longer imitates the lives of the saints, this book may furnish a secular stimulus analogous to that which an older generation derived from godly works.

S. W.

Bedside Diagnosis. By American authors. Edited by George Blumer, M.D. 3 vols. and index. $30.00. (*W. B. Saunders Company, Philadelphia, 1928.*)

Of this system it can be said that the name itself provokes attention. In a medical era that threatens a cessation of essentially clinical study, in a period in which important diagnostic data are elaborated quite out of sight of the patient in question—and often with the patient "out of mind" too—Dr. Blumer comes to us as a medical John the Baptist, reminding us of the simplicity of Salvation. A pleasant kinaesthetic effect is evoked by the contents of these volumes, with their emphasis upon what can be discovered by the unaided senses of the observer.

That the material is of decidedly uneven value does not detract from the importance of the work as a whole. Many of the contributions manifest a lack of clinical vividness—perhaps attributable to the tendency which the editor deplores. But these are more than balanced by numerous chapters which can be read with pleasure.

S. W.

Clinical Aspects of the Electrocardiogram; A Manual for Physicians and Students. By HAROLD E. B. PARDEE, M.D. 2nd ed., revised. 242 pp. $5.50. (*P. B. Hoeber, Inc., New York, 1928.*)

This is the second edition of a particularly well balanced and valuable description of the electrocardiogram—its theory, practical application and significance. The author shows a fine sense of proportion: for a number of years he has seen and emphasized the importance of the photograph of the heart's contraction wave as an aid in the recognition of certain abnormalities of the heart muscle, and it has given the reviewer real pleasure to read this book and find the author, not dallying excessively with the various freakish arrhythmias, but getting down to the real business of the electrocardiogram—the elucidation of clinical problems. Owing largely to electrocardiographic tracings, clinicians have been able to develop clinical criteria that permit recognition of any of the arrhythmias with a reasonable expectation of success. However, as the author emphasizes, the electrocardiogram in many cases is the only objective evidence of myocardial or coronary disease, and he gives this fact its due weight.

We can find no fault with the book and know nothing that could be added with advantage: it is difficult to see how the subject could be handled better. The book can be recommended very highly from every standpoint.

J. T. K., JR.

The Abdominal Surgery of Children. By L. E. BARRINGTON-WARD, Ch.M., F.R.C.S. (Edin.), F.R.C.S. (Eng.). 283 pp. $4.50. (*Humphrey Milford, Oxford University Press, 1928.*)

It has been a pleasure to review "The Abdominal Surgery of Children," by Mr. L. E. Barrington-Ward. This volume is one of the Oxford Medical Publications, and is of interest to a surgeon because it illustrates some of the differences between American and British operative technic. The first chapter on general principles, pre- and post-operative care, is handled in a masterly fashion. Throughout the test the author shows splendid surgical judgment. The chief occasions for differing with Mr. Barrington-Ward's opinions are always in matters of operative technic. This volume is heartily recommended to students because its chief value lies in the terse and accurate clinical descriptions of abdominal lesions in children.

W. M. F.

Pathological Physiology of Internal Diseases. By ALBION WALTER HEWLETT. 787 pp. $7.00 (*D. Appleton and Company, 1928.*)

The present volume, which is the third edition of a well known text, was revised *In Memoriam* by the late Professor Hewlett's colleagues in the Stanford Medical School. The book is sufficiently well known to medical readers to preclude the necessity of a detailed description of its aims and contents. Like the preceding editions, it strives to treat clinical pathological conditions from the functional, *i.e.*, the physiological standpoint. That physiology is the basis for the scientific practice of medicine was emphasized by Claude Bernard half a century ago, and the significance of this relationship has become more obvious with time. It is surprising, therefore, that little effort has been made, so far as textbooks are concerned, to treat clinical medicine from the broad viewpoint of physiology. The physiologist, interested in the purely theoretical aspects of his subject, and the clinician, interested primarily in the practical aspects presented by clinical material, often assume different interests and attitudes towards an essentially identical process. The late Dr. Hewlett, a physiologist by training and a skilled practitioner, attempted to bridge this gap by his text.

Despite the excellent and commendable aim of the editors, the book is not without certain faults. The various sections, revised as they were by different hands, vary in quality. Some include, while others have omitted, very important physiological advances of recent years which have a direct bearing on clinical medicine. Any attempt to condense, in the space of a single volume, a truly complete pathological physiology, with adequate justice to the subject, must necessarily lead to the abruptness characteristic of summaries. This is the most obvious defect of the text.

The book will be of particular interest to the clinician who is unable to cope with the larger physiological texts. The physiologist, too, though disappointed in parts with the physiological material presented, will find much of interest from the clini-

cal standpoint, and will be made aware of many of the practical applications of his subject to clinical medicine.

Fairly complete bibliographical material is appended to each of the sections of the book.

A. G.

The Blood Plasma in Health and Disease. By J. W. Pickering, D. Sc., Lecturer on Hematology, University of London, King's College. (*London, William Heinemann, 1928.*)

There is no more perplexing subject in physiology than the composition and functions of the liquid of the blood. Our knowledge of its chemistry has advanced somewhat, of course, in recent years. The biochemists have developed new methods of analysis which have not only been practically useful in medical diagnosis, but have also thrown some light on the properties of the blood itself, although one may say, perhaps, that this light has served not so much to clear up the main difficulties as to reveal the exceedingly complicated nature of the reactions that take place. The chemical nature of some of its constituents is definitely known, even though their functions for the most part are still obscure, but there are many unknowns, chemically speaking, which are present in almost hopelessly small concentrations, and which nevertheless seem to play an important rôle in the various equilibria that characterize the living state. Our present methods are too crude for the successful analysis of the processes taking place in the blood in health and in disease, but such as they are they must be employed as completely as possible, and the partial results obtained must be used as a basis for our theoretical interpretations.

All students of the blood, physiologists, biochemists, serologists and the specialist in blood-diseases should welcome gratefully this new book upon the subject by Dr. Pickering. Only those who are active workers in the field and know something of its difficulties will appreciate how well he has performed the troublesome task of summarizing our present knowledge. His acquaintance with blood-literature, ancient and modern, seems to be exceptionally complete. In the general bibliography appended to the book there are between eight hundred and nine hundred references to literature, and from the numerous quotations made in the text it would appear that the author has made himself familiar with all the individual researches comprised in this extensive bibliography. He is himself an active investigator in certain phases of the subject, and, therefore, has views of his own upon a number of the problems which at present are matters of discussion, but his treatment of these disputed points is markedly fair and unprejudiced, although naturally certain of his own views are given a greater prominence than might be assigned to them by other investigators.

The central topic of the book is blood-coagulation under normal and abnormal conditions. The factors involved in this process are discussed in detail and the conflicting theories that hold the stage at present are described, and, to a certain extent, are compared and criticized. It may be said that under existing conditions

it is not possible for any one simply by giving thought to the matter, or by making an extensive study of the literature, to arrive at the ultimate truth or even an approximation to it, but Dr. Pickering gives an impartial recital of the facts or supposed facts upon which these theories are based which will be helpful and suggestive to those working in the field. For those not conversant with the peculiar nomenclature of the subject the result of his well-balanced discussion may be less satisfactory. Unfortunately, the points of view and the terminologies employed are so different that it is impossible to formulate many general conclusions that will be accepted by all workers.

While objections might be raised to a number of the arguments and conclusions reached by the author, it must be recognized that he has treated the subject as a whole in an able and scientific way, a sufficiently difficult task when one remembers how freely speculations and observations are intermingled in the extensive literature to be reviewed.

The author's own views are clearly set forth. He holds to the fundamental conception that in the circulating blood there exists an unstable colloidal complex of fibrinogen and prothrombin united in some way also to the serum globulin and albumin, and that this complex must be disrupted by physico-chemical changes before the chemical reactions take place that lead to the formation of fibrin. The evidence for this view is not very direct; it could not well be. It is a theory that is logically defensible, but to the reviewer it seems unnecessary and beyond the possibility of experimental verification. No one has been able to reconstruct such a complex out of the elements of which it is composed.

One of the most interesting sections in the book deals with the important subject of the etiology of thrombosis, particularly after operations and parturition. The author very properly lays emphasis upon the probable absorption of tissue-juice as a significant causative factor under these conditions both as regards the formation of platelet thrombi and the inception of a true clot. He suggests that the absorption may be gradual and cumulative, although to the reviewer it would seem more likely to occur somewhat rapidly during the period of operation. Since there is a general agreement that the active substance in tissue-juice is a phosphatid compound and since certain antigoagulants are known to antagonize the effects of this compound, we may hope that further experimental work will develop a practical method of obviating this dangerous sequela to operations.

In an appendix to the book there is a useful summary of various hemostatics which have lately been proposed, and some of which have been exploited by commercial firms beyond their desserts. One could wish that the author had dealt with these preparations in a more critical spirit, but here again it must be remembered how difficult it is to obtain reliable data in such matters, particularly when it comes to clinical observations which may often be poorly controlled. Even such an apparently simple observation as determining the coagulation time of blood is fraught with so many possibilities of error that results are trustworthy only in the hands of experienced workers.

In the literature bearing upon the problem of coagulation one encounters more than the usual proportion of conflicting results owing to the intrinsic complexity of the processes involved. It is, therefore, fortunate to have a book of this kind, written by one who is so well informed, which gives a reliable account of the present state of our knowledge.

W. H. H.

The Simple Goitres. By Robert McCarrison. 106 pp. $4.00. (*Wm. Wood and Co., New York, 1928.*)

This volume is based on a report, made by the author, to the International Conference on goitre, at Berne, Switzerland, in 1927. The material presented closely follows the chapters dealing with this subject in "Diseases of the Thyroid gland," by the same author. It is stated in the introduction that the book represents a summary of the present state of knowledge of the etiology of simple goitres, *as the author understands it.* Herein, briefly, is the keynote of the whole book. Throughout the entire 106 pages an effort is made to convert the reader to McCarrison's views on the subject. Vague references are made to a multiplicity of ways of producing simple goitre. Similarly, a variety of substances, ranging from cane sugar to stock vaccines are suggested as being curatives. The author states, however, that some of these remedies are enhanced in value if administered along with small doses of iodine! The reader is unable to determine just how well the various experiments described were controlled. Although many references are made to previous works of the author and others, there is no bibliography. The best part of the whole volume is some sixty odd pages of illustrations, among which are many excellent photo-micrographs of normal and abnormal thyroid glands of various species. In short, however, the book is a repetition of McCarrison's well known views on the etiology of simple goitre. For anyone not already familiar with these views, it is a concise presentation of them.

B. W.

Bacteriology and Surgery of Chronic Arthritis and Rheumatism with End-Results of Treatment. By H. Warren Crowe, D.M., B.Ch. (Oxon.), M.R.C.S., L.R.C.P. London, England. 187 pp. $9.00. (*Oxford University Press, 1927.*)

In this volume the author has added much to his "Treatment of Chronic Arthritis and Rheumatism." It contains a comprehensive review of the work of other authors in this field. The author feels quite definitely that the streptococcus is the causative organism in osteoarthritis and that the micrococcus deformans, a form of staphylococcus, is responsible for rheumatoid arthritis. Weston Price's book on dental infections is quite well reviewed, and a number of interesting dental x-rays have been reproduced. The author's end-results after vaccine treatment are given. He shows that in 450 cases of chronic arthritis improvement was obtained in 68 per cent, and in 186 non-articular rheumatic cases there were good results in 80 per cent. The chapter on the Surgery of Joints in Arthritis by Herbert Frankling is

extremely good. The bacteriological technique with a description of the preparation of the media is discussed in detail. There is also a chapter on the classification of streptococci with most complete charts. Special mention should be made of the beautiful colored reproductiont of bacterial growths on media. The book is a distinct contribution to the study of arthritis.

A. R. S., Jr.

Local Anesthesia. By GÉZA DE TAKÁTS, M.D., M.S. 221 pp. $4.00. (*W. B. Saunders Company, Philadelphia and London, 1928.*)

Although the widely known books of Labat, Braun, Farr, Finsterer and others cover all phases of this subject, there remained a definite need for such a presentation as this recent monograph by de Takáts. The author received his surgical training in the University of Budapest and is now Assistant Professor of Surgery in the Northwestern University Medical School. As he states in his preface, his book represents a course which was first given to postgraduates, and is now offered to senior medical students. It is offered as a guide to the more voluminous works on the subject.

The present tendency appears to regard local anesthesia not as a surgical specialty, but rather as an indispensable part of a surgeon's technical equipment. Its increasing use has done much to develop standardized methods which in many clinics are a part of the surgical training. Those interested in a concise and well illustrated presentation of these methods will find this book most satisfactory.

E. M. H., Jr.

Neoplastic Diseases. A Treatise on Tumors. By JAMES EWING, A.M., M.D., Sc.D. Third Edition. 1127 pp. $14.00. (*W. B. Saunders Company, Philadelphia and London, 1928.*)

This third edition contains a number of noteworthy changes. It is pleasing to find the classification of brain tumors, bone tumors, and of breast cancers simplified. The bibliography, as formerly, is especially useful.

The first part of the book gives an interesting summary of our information on such general topics as the historical development of the knowledge of tumors, the effect of malignant tumors on the organism, the various theories pertaining to the cause of tumor growth, and experimental cancer research.

As it is stated in the preface that the object of the work is to present the main features of the origin, structure, and natural history of tumors, such inflammatory conditions as Hodgkin's disease might very well have been omitted from treatises on neoplasms; tuberculosis might have been included just as appropriately.

Throughout the book, in the discussions regarding the aetiology of tumors, one finds a variety of causal factors suggested with a degree of confidence which does not seem justified by the evidence. It is stated, for example, that the majority of bladder cancers are caused by cystitis. The relation between Bilharzia cystitis and some bladder cancers seems clear enough, but a causal relation between a majority of these tumors and cystitis is far from certain. Again, it is suggested that stag-

nation of milk may be the central factor in the production of carcinoma of the breast. Certainly one cannot say with assurance that it may not be a factor, but the simple fact that carcinomata occur in breasts which have never lactated is significant evidence to the contrary. And we know of no other case where obstruction of the ducts of a gland causes the growth of a malignant tumor. The paragraph on the aetiology of "Simple Lymphoma" leads one to believe that there is good evidence to show a causal relation between tubercle bacilli and the tumors with the structure described under the term, "Simple Lymphoma." The statement is made, too, that tuberculosis occupies a prominent position as an excitant of lymphosarcoma, and it is said that tuberculosis is the chief aetiological factor in the production of carcinomata of the lung.

The fallacy in all of these examples is the same. From the association together of two conditions, one obscure, the other clearly understood, one of the two, always the simpler, is arbitrarily chosen as the cause of the mysterious neoplastic process. It should be pointed out that accurate deductions can be drawn only by examining a large number of the suspected causal factors for the constancy with which they are followed by, or associated with, or appear to cause, the other obscure condition. It then becomes obvious from the experimental and clinical study of tuberculosis, for example, that its infrequent association with lymphosarcoma is as coincidental as is its association with Hodgkin's disease, simple lymphoma, carcinoma of the lung, diabetes mellitus, exophthalmic goitre, or any other accidentally related disease.

S. S. B.

The Mechanics of the Digestive Tract. An Introduction to Gastroenterology. By WALTER C. ALVAREZ, M.D. With one hundred illustrations. Second edition. 447 pp. $7.50. (*Paul B. Hoeber, New York, 1928.*)

This book represents a happy attempt to bring together the world literature concerning various intricate problems in gastro-enterology. The author includes in more or less detail his own research efforts in this field. Here and there, at the conclusions of the presentation of conflicting and confusing data, he steps in to summarize and to offer an opinion as to what one might believe in the light of available information. Alvarez is an ardent advocate of the myogenic theory, and offers much evidence in its support; and his long and laborious service in this avenue of investigation enables him to speak quite authoritatively.

In this work one is impressed with Alvarez' exposition of his gradient theory. He defines a gradient to be a "gradation between certain limits in time or space." There are gradients of rhythmicity, chemical activity, tonicity, irritability, structure, electrical potential, and force. The rhythmic gradient is seen from pylorus to colon: it varies from 17 times per minute in the duodenum to 10 times in the ileum; that there is a definite gradation in the chemical processes which underlie rhythmic activity is evidenced by the greater consumption of oxygen in the duodenum than in the ileum and a gradation in carbon oxide production from duodenum to colon. The tone of the duodenum is more marked than that of the ileum so that the "tendency

of guinea-pig intestine to contract more at the cephalad end than at the caudad suggests that this gradient of tone accounts for the direction of peristalsis." The gradient of irritability is greatest in the duodenum, for it is more responsive to distention by gases or food. In anatomic structure there is a gradation in the thickness of the muscular coat of the small intestine from duodenum to the ileo-caecal valve. A gradation in the nerve and blood supply is seen from the duodenum to the ileum. In regard to the stomach, the author shows that in animals the lesser curvature next to the cardia is more rhythmic, more tonic and more irritable than the middle third and more so than the pylorus. Alvarez feels that gradients of electrical potentiality are produced within the tissues themselves. This gradient idea is also applied to the heart where the author attempts to show that the beat follows a gradient of rhythmicity—from sinus to ventricle. There is an interesting chapter on "Practical Considerations of the Gradient Idea."

Evidence obtained by means of the electrogastrograph in animal studies shows that the problems of gastric peristalsis are more complex than is indicated by roentgenologic observations. Alvarez presents tracings showing waves starting anywhere and everywhere over the surface of the stomach, all of which travel toward the pylorus, although sometimes there seems to be a marked "dissociation between the activities of the fundus and the pars pylorica."

An excellent summary of vast material appears in the chapter on "Hunger Contractions and Pain of Ulcer." The chapter on the "Modus Operandi of a Gastro-Enterostomy," indicates that while none of the explanations for the relief secured from this operation are entirely satisfactory, Alvarez' analysis of experimental evidence and clinical studies indicates that the lessening of the strain on the pylorus and a lowering of gastric acidity are jointly responsible for some measure of relief.

The chapters on "Reverse Peristalsis and their Symptoms," "Vomiting," "Flatulence," "the Rate of Progress of Food Residues," are illuminating. There is an excellent bibliography appended. To those interested in gastro-enterologic research there is a chapter on technical methods and apparatus. Incidentally, Alvarez urges the use of motion pictures in the study of these problems. Throughout the book are scattered the likenesses of some of those whose efforts have added much to our knowledge in this field.

This is an excellent book. It should find a place in the libraries of all interested in gastro-enterology either from a clinical or experimental standpoint.

M. P.

BOOKS RECEIVED

Operative Surgery. By J. SHELTON HORSLEY, M.D., F.A.C.S. With 756 original illustrations. Third edition. 1928. 4°. 893 pages. The C. V. Mosby Company, St. Louis. $15.00.

The Duodenum. Medical, Radiologic and Surgical Studies. By PIERRE DUVAL, JEAN CHARLES ROUX and HENRI BÉCLÈRE. Translated by E. P. Quain,

M.D. 1928. 8°. 212 pages. The C. V. Mosby Company, St. Louis. $5.00.

A Handbook of Clinical Gynecology and Obstetrics. By RAE THORNTON LA VAKE, A.B., M.D., F.A.C.S. Illustrated. 1928. 8°. 281 pages. The C. V. Mosby Company, St. Louis. $4.00.

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